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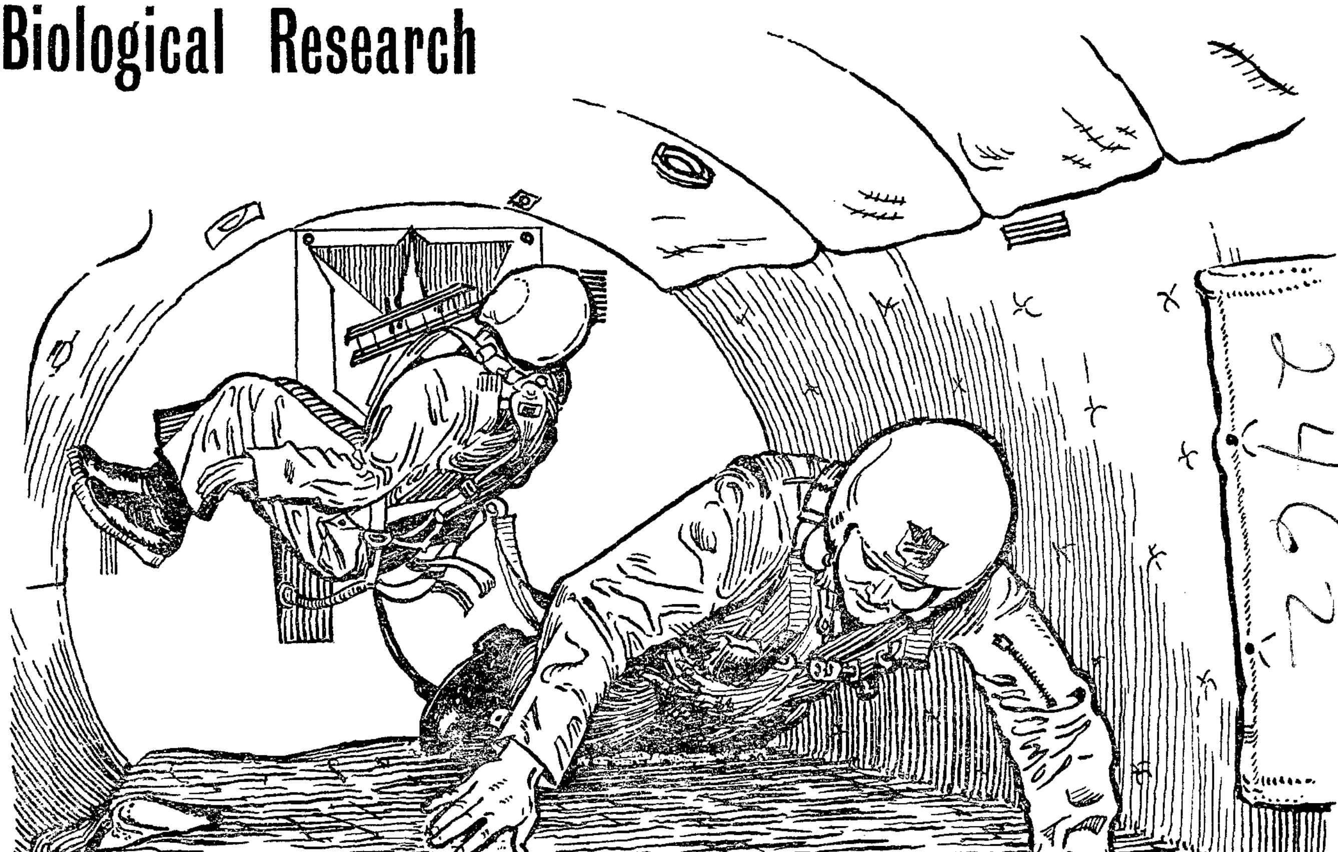
A Survey of Chronic Weightlessness Simulation In Biological Research



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HQARSC-TDR-64-1

A SURVEY OF CHRONIC WEIGHTLESSNESS SIMULATION IN BIOLOGICAL RESEARCH

Directorate of Bioastronautics
Headquarters, Air Force Systems Command
Andrews Air Force Base
Washington 25, D. C.

Prepared under Contract No. AF 18(600)-2057
University of Virginia
Charlottesville, Virginia

20030110 132

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A SURVEY OF CHRONIC WEIGHTLESSNESS SIMULATION IN BIOLOGICAL RESEARCH

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Prepared under Contract No. AF 18(600)-2057
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FOREWORD

In analyses of the probable biomedical effects of extended orbital flight on USAF personnel the influence of weightlessness has generally been predicted to be of great significance. The loss of weight cues, the drastic diminution of muscular effort required, the reduction of sensory "bombardment" of the nervous system, possible effects of the lack of gravity, *per se*, on cellular mechanisms, and several other postulated events have all been considered likely to have direct or indirect effects on body well-being and efficiency. Although completely valid simulation of the "weightless" state has not yet been possible on the Earth's surface, and actual orbital flights have been limited to a few day's duration, several partially analogous experimental situations have been exploited to study some special aspects which may prove characteristic of the weightless state. Among these are prolonged, quiet bed-rest, and water flotation. One technique which does not appear to have been carefully considered in this connection is body and/or limb immobilization. Rigid, long duration immobilization of part or most of the body, as for example by traction, casts, splints, or restraints of other types may in some respects simulate weightlessness in the degree to which body movement, muscle contraction, and energy expenditure are all severely limited. A survey and critical evaluation of available scientific biomedical literature and any on-going research in this general area, from the particular point of view of the possible similarity of such a "hypo-activity" situation to weightless condition, might therefore reveal highly informative clues for prediction or further study of the hypothesized effects of the zero-gravity state.

The University of Virginia was authorized and directed to carry out the review and critique of the existing state of scientific knowledge concerning neurological, muscular, skeletal, and peripheral vascular effects of such severe states of body arrest as those described above.

Publication of this technical documentary report does not constitute Air Force approval of the report's findings or conclusions. It is published only for the exchange and stimulation of ideas.

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The opinions and conclusions in this report are those of the author, and are not to be construed as necessarily reflecting the views of the Air Force Systems Command. This report is approved for publication to provide a broad dissemination of the information it contains.

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A SURVEY OF CHRONIC WEIGHTLESSNESS SIMULATION IN BIOLOGICAL RESEARCH

I. INTRODUCTION

The singular fact about weightlessness is that, although its physical principles are well understood, no adequate simulation of it exists. Investigators are forced to approach this problem by various indirect methods. Like many of the problems currently being explored in our space effort, basic biological considerations of weightlessness were largely ignored until interest in space travel became fashionable.

A. Historical Background

As gravity is one of the factors of our environment which undoubtedly influences many biological processes, the reduction or absence of this influence would be expected to have far-reaching effects. In spite of the constancy and persistence of gravity throughout evolution and development upon this planet, its biological implications have been sparsely investigated. It has always been taken for granted and therefore ignored. Now with the dawning of space travel, man is forced to consider those problems of weightlessness which, until recently, were considered of such an academic nature as to be undeserving of practical consideration.

Gravity has always been a force which could potentially influence life during the four billion or so years that life has existed on Earth. When the organisms on this planet were no larger than the single cells existing in the ancient seas, however, buoyancy negated gravitational effects, so that, in effect, the very early life-forms existed in a nearly weightless environment. The primary effect of gravity was that of stratification or sedimentation of the organisms themselves, with the still unsettled possibility of similar influences within the individual cells. Although the gravitational influence would become more pronounced as larger organisms evolved, buoyancy due to water would continue to simulate a nearly weightless environment. The first major withdrawal from weightlessness occurred when plants or animals deserted the ocean's buoyancy and attempted to exist on land. Insects attempted to live on land approximately four hundred million years ago. They were followed after another hundred million years by the primitive amphibians. The early reptiles, which came still another hundred million years later, were the first of our ancestors to exist independent of buoyancy. Even so, they were still imprisoned against the Earth's surface by gravity.

Birds and other animals which developed the ability for flight represent a step in the successful opposition to gravity. Man's erect posture and later technical developments represent other such steps. Man still starts each new life with the near weightless environment simulated by suspension within the womb, and he now aspires to the weightlessness which awaits him in outer space.

The history of man betokens a long line of technical developments (such as the wheel, invented seven thousand years ago, and later other devices) which worked to oppose the gravitationally imposed friction. It was not until a few hundred years ago, however, that man began to develop an awareness of the existence and nature of gravitational forces.

The first appreciation for gravity probably came with Galileo, who, by the turn of the seventeenth century, had described its influence upon falling bodies and noted its role in limiting the size of animals (Thompson, 1942, p. 27). There were also the seemingly unrelated theories describing planetary motion which had been made by Copernicus a hundred years previously and which, at Galileo's time, were being described in more mathematical detail by Kepler. The relationships between Galileo's observations of gravitational phenomena and motion upon this planet and the relationship to astronomical observations were finally elucidated by Newton in his *Principia* in 1687.

The first experimental demonstrations that gravity or other inertial fields do indeed influence life were those performed by Knight in 1806. His studies involved the discovery that the growth of bean plants was not oriented with respect to the direction perpendicular to the Earth's horizon but rather to the direction of an inertial field. In Knight's experiments, this field was the vector sum of the Earth's gravity and the centrifugal field generated within a water-driven centrifuge.

The first attempts to simulate a weightless environment also were performed with plant material. The work by Sachs in 1872 (as cited by Lyon, 1962) and the later work of other botanists involved rotating or tumbling plants in a device known as a klinostat. The klinostat tumbles plants with their axes of growth at right angles to the gravitational vector with a speed of rotation such that the direction of any settling within the plant cells would be constantly changing, thereby eliminating any net gravitational effect at the cellular level.

The history of the study of weightless phenomena with animals has recently been reviewed by Generales (1963). One of the earliest observations that normal gravity can influence biological processes was that of Pflüger (1884, as discussed by Morgan, 1897), in which the direction of cleavage in the frog's egg was observed to be dependent upon its orientation with respect to the Earth's gravity. A decade later, Schultze (1894, as discussed by Generales, 1963) noted that when the fertilized eggs of the frog, *Rana fusca*, were inverted abnormal development ensued. Megusar (1906, as discussed by Generales, 1963) made comparable observations with the water beetle, *Hydrophilus arterrimus*.

For eighty years, then, man has known that gravity influences the normal growth of animals. In spite of this seemingly profound realization, studies of the prolonged influence of an altered gravitational state have been sadly neglected until the present spectacular interest in space travel.

Strughold in 1928 (as discussed by Hawkins, 1963), with short bouts of weightlessness as simulated by opposing acceleration in aircraft, was the first to make observations with man. His studies were concerned with the overshoot in positioning or aiming as a result of the absence of gravitational cues. During the two decades following, as the performance of aircraft improved, people occupied with problems of aviation became more concerned with the influence of high or low gravitational environments.

The first non-experimental situation in which men were required to perform tasks during weightlessness occurred during World War II (Bourne, 1963). German fighter pilots executed a maneuver in which they first dived from above to beneath allied bombers. They then executed an outside loop, counteracting the Earth's gravity by a centrifugal field as they swung up to attack the belly of allied airplanes.

With advances in their rocketry, German scientists began to consider the implications of prolonged weightlessness which might accompany space flight. Mindful of the changes in the sensory threshold for other agents in our environment, they (Gauer and Haber, 1950) warned that in the absence of the Earth's gravitational field the slightest of movements could generate inertial fields which, although tiny, would be capable of quickly disorientating human subjects. They explained this prediction in terms of the Weber-Fechner Law, which predicts that the detectable change in intensity of some stimuli varies in direct proportion to the initial intensity of that stimuli or agent. It was known even at that time that some disorientation could occur during the first few seconds of weightlessness. Fortunately, it has since been found that man can, after a few seconds, adjust to weightlessness. The dire complications to be expected if the range of applicability of the Weber-Fechner Law extends to the very low gravitational intensities are not now apparent. Although time has proved their warnings to be of an overcautious nature, Gauer and Haber did suggest a potential threat which required elucidation before any manned space flight program could proceed with confidence. Their paper still stands as a classic.

Near the turn of the present century, such neurophysiologists as Sherington and Pavlov began to explore the nature of various nervous reflexes. One would expect many reflexes to be indirectly influenced by the forces exerted either by gravity or by the muscles which oppose gravity. The manner in which they might function in the face of the lower forces and lower energy demands to be expected in a weightless environment has not been thoroughly investigated. By the time of World War II, seemingly unrelated studies were under way. These were stimulated by an interest in obtaining information basic to the deconditioning associated with poliomyelitis, muscular dystrophy, immobilization, and bed rest (Eccles, 1941, 1944; Hines *et al.*, 1943; Hines and Thomson, 1956).

Since the beginning of recorded history, rest and various degrees of immobilization have been the most commonly employed forms of clinical therapy. Ironically, until recent years little attention has been given to the influence of such hypoactivity upon man's normal physiology. Concern for the possible adverse effects of prolonged bed rest or immobilization with men being treated for battle injuries stimulated investigations with relatively small samples of conscientious objectors subjected to prolonged bed rest at the University of Minnesota (Taylor *et al.*, 1945; Taylor *et al.*, 1949) and at Cornell University with plaster-cast immobilization (Deitrick *et al.*, 1948; Deitrick, 1948; Whedon *et al.*, 1949). There was also concern that prolonged lack of muscular and gravitational force upon bone could result in demineralization and the eventual formation of kidney stones (Flocks, 1945; Cockett *et al.*, 1962).

In the years immediately following the Second World War, Henry and co-workers (1952) studied the effect of weightlessness as simulated by means of suborbital flight in high altitude rockets. They employed captured German V-2 rockets and later American Aerobee rockets. Using electrocardiograph and respiration studies with mice, they concluded that weightlessness had no significant effect upon this animal. Disorientation in mice was observed, but since it did not occur in those animals in which the middle ear had been destroyed, it was concluded that disorientation came from a lack of stimulation of the otolith organs in animals which had not learned to depend upon other sensations for orientation. It was concluded that no adverse effects would result from bouts of weightlessness lasting no longer than two or three minutes.

In Argentina, and later in this country, von Beckh performed studies with turtles and men during weightlessness simulation in aircraft (von Beckh, 1954, 1959). He noted that normal turtles (unlike labyrinthectomized turtles) and men in the weightless state tended to overshoot when reaching or aiming for targets. This overshoot phenomenon was confirmed by Gerathewohl *et al.* (1957), with the indication that individuals could adjust for overshoot after continued exposures to short bouts of weightlessness. In conjunction with these studies, von Beckh made another interesting observation. A very brief exposure to weightlessness, he noted, would decrease man's tolerance to the high gravity which immediately followed and which was indicated by onset of visual blackout.

After the early work of Henry and his co-workers, rocket studies with animals were discontinued in this country until 1957. Rocket studies with dogs, however, were being actively pursued by the Russians (Henry *et al.*, 1952, 1962; Kousnetzov, 1958; Kas'yan, 1963).

Throughout the early nineteen fifties, save for modest, small-scale investigations, most research which was admittedly pertinent to problems of space biology or weightlessness was overlooked if not actively discouraged. It was risky business still for scientists wishing to maintain their reputations to admit an interest in space travel.

It is generally agreed that no entirely adequate simulation of a weightless environment is presently possible upon the surface of this planet. Before satellites became a reality, studies involving the prolonged exposure to an altered gravitational intensity were possible only with a simulated high-intensity, though not with a low-intensity, field. This involved the exposure of organisms to chronic centrifugation. Reference has already been made to Knight's studies with bean seedlings at the early part of the nineteenth century. Save for the publication by Hertwig (1899), there was no continuation of such studies for almost a century and a half.

Approximately ten or fifteen years ago, people on several campuses became interested in demonstrating experimentally that quantitative relationships exist between the magnitude of the Earth's normal gravity and the development of various organisms. Centrifugation served to exaggerate a normal gravitational influence. At Emory University, studies were pursued with wheat seedlings (Miller, 1950; Gray and Edwards, 1955) and, more recently, with plant and animal cells in tissue culture (Edwards, 1963). At Cambridge University, rats were grown for periods of several generations during continual exposure to 3 G (Matthews, 1953). At the State University of Iowa, studies were initiated with fruit fly larvae (Wunder, 1955) and, more recently, with mice, hamsters, turtles, fish, chameleons, and grasshoppers (Wunder *et al.*, 1963; Wunder and Lutherer, 1964). At the University of California at Davis, studies were pursued with chickens and turkeys (Smith *et al.*, 1959; Smith and Kelly, 1963).

In the mid nineteen fifties, men were subjected to certain aspects of weightlessness by means of water immersion. These studies dealt with sensory deprivation. By 1956, it was known that if the tactile sensations for gravity, together with certain other sensations, were reduced to a minimum, various psychological disorders could occur (Lilly and Shurley, 1961).

Even though announcements were made by both this country and Russia to the effect that artificial satellites would be placed in orbit for the purpose of collecting physical data during the International Geophysical Year of 1958-59, the likelihood of space travel seemed remote—almost as remote as the possibility that Russia might possess a space technology comparable to our own, however long neglected the U.S. space program might be. Only the shock of the Russian achievements in 1957 forced the realization that the space age was here. Finally people realized that if this country were to remain foremost in the community of nations it must begin to investigate what will happen to man when he leaves the Earth's gravity.

As was the case with other aspects of space science, studies of the biological implications of weightlessness were forced to expand at a disorderly rate. Investigators in the field have been unable to keep adequately abreast of the progress. Publications are obsolete almost by the time they appear in print. Weightlessness studies possess a handicap, moreover, which is not characteristic of most problems of the space program. No adequate means exist for removing gravity from Earth-bound laboratories, and all methods of simulation have serious deficiencies.

B. *Scope and Purpose of This and Related Reviews*

1. *The Present Review*

This review is primarily concerned with the evaluation of approaches which attempt to predict the influence of prolonged weightlessness. The original understanding of the reviewer was that this survey ought to encompass an evaluation of the status of various approaches whereby chronic weightlessness can be simulated. After the survey was planned and initiated, the Air Force requested that the survey be concerned primarily with those approaches which involve immobilization. Since the survey was already under way, and since the evaluation of one approach would depend upon the comparative advantages of other approaches, it was decided that the survey would encompass all approaches. This would permit comparison of the status of other approaches with that of those which involve immobilization.

The survey will evaluate the various approaches to weightlessness from the perspective of their influence on the biological systems under consideration. Performance and kinesiological considerations which do not bear directly upon the biological response of the organism are beyond the scope of this survey.

2. *Influence of Inertial Forces*

Probably the best considerations of the natural influence of gravitational fields upon plants and animals is presented in D'Arcy Thompson's book on *Growth and Form* (1917, 1942). This book should almost be a bible for anyone concerned with the natural history of gravity's influence upon growth and development. Gauer and Zuidema (1961) have edited a book containing a series of papers devoted primarily to acute exposure to high gravity. The author of the present survey has prepared a short review dealing with the influence of both high and low fields upon organisms (Wunder, 1963).

3. *Symposia on Weightlessness*

Two symposia on weightlessness have been printed (Benedikt, 1961; Benedikt and Halliburton, 1963). They were sponsored by the American Astronautical Society and were intended to permit an exchange of current thinking about both the physical and the biological influences of zero gravity.

4. *General Reviews of Biomedical Implications of Weightlessness*

There have been a number of good general reviews.[†] Some of them have been published (Gauer and Haber, 1950; Lansberg, 1960; Lawton, 1962; McCally and Graveline, 1963a) or are about to appear (Lawton, 1964). Unfortunately two very good reviews have appeared only as government reports: the first, a review by Vinograd (1962), is designed for those readers unfamiliar with basic biological and medical terms and considers both the biological and physiological effects not only of weightlessness but also of rotation; the other is by Lawton and McCally (1963) and probably is the most comprehensive review for the physiological aspects of weightlessness. Loftus and Hammer (1961) have reviewed the psychological aspects of weightlessness. Gerathewohl (1961) has reported some of the weightlessness simulators which were proposed or in use by 1960. There are several other reviews which are primarily concerned with only limited approaches to the problem of weightlessness and will be considered separately in the next part of the paper (pp. 15-60).

5. *Compilations of References or Abstracts*

A complete citation of all articles referred to in the preparation of this survey would be impractical due to limitations of space. References to individual studies will be limited primarily to those not cited in reviews mentioned at this time. Probably the best source for locating articles dealing with the biomedical problems of weightlessness is the abstracts section which appears in each issue of *Aerospace Medicine*. Another appropriate abstracting source, one which has only recently been initiated, is the *Scientific and Technical Aerospace Reports*. It is a semi-monthly abstract journal with indices published by the Office of Scientific and Technical Information of the National Aeronautics and Space Administration, Washington, D.C. There also has been a recent listing of various government reports and translations (OTS, 1963), which is distributed by the U.S. Department of Commerce. Slightly more than a year ago, Price (1963) prepared another compilation of abstracts.

The Air Force is presently preparing what will eventually amount to an encyclopedia of pertinent information on all aspects of weightlessness. It is not confined only to biomedical areas; basic physical areas are also included. Certain sections of this work are now available (*Handbook*, 1963).

[†]Information has recently been received that an extensive review of original and published data comparing the effects of weightlessness upon six Soviet and six American astronauts has been published but presumably not yet translated from Russian: Yazdovskiy, V.I., Kas'yan, I.I., and Kopanev, V.I. (1964). "Physiological Reactions of Cosmonauts to Periods of Excess Weight and Weightlessness," *Izvestiya Akademii Nauk SSSR, Seriya Biologicheskaya*, No. 1, pp. 12-31.

As a result of various factors, including the language barrier, most of the Russian literature is relatively inaccessible to the average reader. As is the case with other areas of space biology, some of these articles are translated by the U.S. Joint Publications Research Service, and are now available in a few of our larger libraries. Of the articles available, many appear to have been written by the Soviet equivalent of a public relations officer. They give glowing accounts of the experiments performed and of the types of variables which were measured. With respect to the exact nature of the results obtained, however, they are somewhat evasive. In part, this is attributable to the fact that the popular and semi-technical articles from Russia can be more readily obtained by our information services. A number of articles of a more technical and informative nature appear in the book titled *Problemy Kosmicheskoy Biologii* [*Problems of Space Biology*], edited by Sisakyan and Yazdovskiy (1962).

6. *Muscle and Nerve*

There have been two reviews which are primarily concerned with the neuromuscular aspects of weightlessness. Both are elementary and informative articles intended for readers who do not necessarily have a good background in biological areas. These are a published article by Bourne (1963) and a report by King *et al.* (1961).

C. *Results to be Expected from Weightlessness*

What one might expect to happen with a living organism during the prolonged absence of gravity is still largely a matter of conjecture. The predictions are based upon limited experiments in spacecraft and other perhaps even less satisfactory approaches. A brief description of some of the possibilities will be discussed in the ensuing paragraphs and is outlined in Figure 1. References to the source of some of these conjectures are listed in Table I and will be discussed in somewhat more detail in Part II of this survey.

With a decrease in the effective gravitational field, the weight (*i.e.*, the gravitational force or the product of this field intensity and that of the mass of various bodies under gravitational influence) will decrease. In the complete absence of inertial field, any mass would be weightless. From a consideration of the methods whereby the effects of reduced weight can be simulated without the removal of the field, one may consider two types of gravitational force. The first of these concerns the forces of weight which are acting directly upon the body. Certain aspects of weightlessness may be simulated if the effects of these forces are reduced by better support in positioning to oppose gravity or by restricting the activity of the animals so that less effort is required to oppose gravity. The second type concerns those forces which will act within the body of the organism and thus cause internal displacements, settling, and the distension of its integument.

For the forces resulting from the weight of materials possessing a density essentially the same as that for water, some gravitational influence can be reduced by whatever measures will prevent distention of the integument. Those constituents of the organism which possess the same specific gravity as body fluid will be supported by buoyancy. Distention can be prevented or reduced by whatever measures will equalize the net pressure differences across the walls of the integument. As hydrostatic pressure increases with the height of a column, recumbency will more closely resemble the weightless state than does the sitting or standing posture. Application of tight garments will prevent distention of the body by providing an essentially greater tension for the body walls. Finally, immersion in water itself will provide buoyant forces with hydrostatic pressures on the outside of the body counterbalancing those within the body.

Great difficulty is encountered in nullifying forces acting within the body when density is different from that of body fluids. As the more dense materials tend to sediment toward the bottom of the organism, structure, or system, while the lighter of the less dense material tends to float toward the upper portions of a system, continual tumbling can often reduce the net amount of settling possible.

It is reasonable to assume that in the absence of the taxing effects of gravity certain adjustments will be made. Perhaps it might be more accurately stated that the body will fail to maintain the adjustments normally necessary in the presence of gravity. This deconditioning could eventually result in an organism which would be less able to sustain gravitational forces. Even though an astronaut may be able to tolerate the Earth's normal gravity, this deconditioning might place him at a serious disadvantage during the period of intense deceleration which accompanies the return into the Earth's atmosphere.

Developmental changes would be expected. Structures which experience a reduced functional need might also experience a reduced growth or even a net loss in size. With less food required for energy to oppose gravity, more food materials might be available for growth, particularly with respect to body fat. If appropriate procedures are not taken to prevent this deconditioning, the result may be an obese weakling.

1. *Less Force Acting on the Body*

With less energy required to oppose gravity, there would be not only the altered physical development. A surplus of available energy might cause certain mechanisms which would normally preserve energy to fall into disuse. A decreased efficiency might persist when the animal does need more energy.

With the decreased force to stretch or strain muscular and tendon tissues, there would be a decreased stimulation of sensory perceptors within these structures. Altered thresholds of response by these receptors and altered postural reflexes for equilibrium could result. The decrease in the force to stretch muscles and tendons would not only come from the direct decrease in gravitational force but also from the reduced need for muscular contraction. Decreased muscular and gravitational forces would also mean that there would be less than normal skeletal strain. Moderate strain (or the resulting mechanical stress) is believed to be one of the factors responsible for stimulating and directing the growth of bone (Thompson, 1942, pp. 958-1025; Sissons, 1956). The rate of bone anabolism being slower than the rate of bone catabolism, there would be an excretion of extra calcium and phosphorus. If critical high urine levels of these minerals persisted, kidney stone formation could occur.

The decrease in muscular work to oppose force would not necessarily mean a decrease in muscular movement. For this reason, any mimicry of weightlessness involving immobilization would not be an accurate one. As in the case of immobilization, the muscles doing less work would decrease in size and in ability for maximum exertion of force. With the greater ease of body motion, greater isotonic contraction of the muscle could occur, so that an individual exposed to weightlessness might possess muscle which, although smaller than normal, would still possess a greater ability for light muscular work than would muscle which had been completely immobilized (Elliott and Thomson, 1963). On the other hand, as the work of Elliott and Thomson showed (at least with the gastrocnemius of the rat), exercises which permit muscle shortening are necessary in order to maintain the best ability for light work. A program of conditioning which includes only static exercise ("dynamic tension" or isometric contraction) might not be adequate for extended space voyages.

2. *Forces Resulting with Material of the Same Density as Water*

With the lowered pressure differences across both the integument of the body and the walls of such structures as blood vessel, decreased distention of all these structures would occur. With a slightly greater than normal net pressure across the walls of the blood vessels, a small amount of transfer of fluid from the blood into the tissue might occur. This trend toward a decreased blood volume would undoubtedly be reversed by slower but more potent processes. With the lower pressure gradients to oppose the return of venous blood to the heart, it would return more readily and distend the auricles. It is believed that this would stimulate certain volume receptors which have been proposed for the walls of the heart's auricles (see reviews by Smith, 1957; Pearce, 1961; and Gauer and Henry, 1963). These sensory receptors for volume would reflexively cause a decrease in the amount of antidiuretic hormone (ADH). This would result in a faster rate of urine formation from the kidney. There would be a decreased blood volume, a greater hematocrit, and a greater thirst. If the thirst could not be satisfied, dessication of the body could also occur. Whether or not reflexes arising from auricular volume receptors might also influence the electrolyte secretion by the kidney is an unsettled question (Smith, 1957; Davis, 1962; Farrell and Taylor, 1962; Gauer and Henry, 1963). With decreased work by the animal and with the lesser forces required to oppose gravity, the heart would be called upon to exert less pressure. A decreased stimulation of sensory receptors for pressure in the circulatory system, together with a decrease in the other efforts necessary for maintaining satisfactory circulation, could result in a decreased sympathetic or animate activity of the autonomic nervous system. Less noradrenalin would be released. The blood vessels would more readily distend should high pressures result from a sudden return to a gravitational environment.

This type of cardiovascular deconditioning has been most frequently tested by means of a tilt table. This involves suddently tilting a person from a recumbent to an erect or nearly erect position in the Earth's gravity. The deconditioned individual should resemble those people possessing orthostatic hypotension. With both the decreased blood volume and lessened tension in the walls of the blood vessels (particularly of the veins, beneath heart level), pooling of blood would occur with less blood returning to the heart. With less blood returning to the heart, the arterial blood pressure would drop, and pulse rate would increase in an attempt to correct this condition. If cardiovascular adaptation is not adequate, the blood could supply less oxygen to the brain and fainting would occur.

3. *Forces Resulting from Density Differences*

Since air has a density drastically different from that for water, certain changes might be expected in the ventilatory respiration as well as the distribution of blood in the lungs. Erect individuals normally receive gravitational assistance in pulling the viscera down as the diaphragm contracts. The absence of gravity would therefore tend to immobilize the diaphragm. If the major ventilatory effort is eventually met by intercostal breathing, some diaphragm atrophy could result. This might be enhanced by a lower total expenditure of energy and therefore less demand for oxygen.

With the decreased settling of the calcarious otolith particles in the utricle of the inner ear, some disorientation would occur. This disorientation could be compounded by lack of sensation arising from the sensory-end-organs for stretch, strain, and pressure from other parts of the body. This as well as the possible unnatural distribution of gases and liquids within the various parts of the digestive tract (von Beckh, 1963; Combs, 1962) could cause nausea.

The possibility for decreased sedimentation and stratification has been considered as a possibility for causing effects even at the cellular level (Wunder and Lutherer, 1964; Pollard, 1962). With animal cells at least, this possibility seems remote. The smaller a structure, the more mechanically stable it is and therefore less likely to be influenced by the existence of or change in gravitational intensity. Random forces, such as those associated with diffusion, moreover, are likely to cause redistribution of material faster than it would be sorted normally by gravitational fields. Nevertheless there is some feeling that a different distribution of structures (*e.g.*, the mitochondria) could occur in some of the larger plant cells.

D. *Misleading Terminology*

There are a number of terms which are conventionally employed with reference to our one-G environment. Since they are proportional to each other in this constant gravity, our experience would unjustifiably tend to treat them as equivalent terms. Although this inaccuracy is of little consequence on the Earth's surface, confusion will exist if such imprecise thinking is extended to considerations of an altered gravitational environment. Differences between mass, fields of force, force, and weight gain new significance in the altered physical context. Various pressures and frictional forces related to an object's weight would be different. Some of these considerations are described in more detail elsewhere (Wunder and Lutherer, 1964).

When one considers the extent to which immobilization and decreased activity might cause the same effects as true weightlessness, it becomes necessary to differentiate between *motion*, *movement* or *momentum*, and *work*. *Motion* or *momentum* has reference to the rate at which mass is being moved and should be thought of in terms of the product of a body's mass and of the velocity at which the mass is being displaced. As motion is expressed in terms of the body's mass rather than its weight, the same velocity displacement would result in essentially the same movement in different gravitational fields. On the other hand, *work* refers to the product of displacement and force required to achieve displacement. The work which is used to move a weight against gravity would, for the same amount of displacement, increase with gravitational field. Although there would be certain non-gravitational forces to overcome, the absence of gravity would yield an overall reduction in the total amount of energy necessary to execute most movements. Many, though not all, frictional forces depend upon gravity. Thus in the absence of gravity, considerably less force would be necessary in the sliding of objects. Inevitably the work requirements for many operations would be reduced. With reduced gravitational friction, however, some new force would be necessary to effect the anchoring of men when they are turning knobs and pushing levers. In some instances, the extra work which a person might have to exert in performing the anchoring necessary for certain operations would cause a total increase rather than decrease in the amount of work necessary.

The term *activity* is a more general term which is more frequently used to refer to either the motion or the work which an organism executes. The decreased activity of an immobilized individual in an Earth-bound laboratory probably would not be the same as that of an individual in space who is readily able to make certain movements but is not required to overcome great forces or to expend much energy in performing those motions.

Stress is another confusing term. In mechanical considerations, stress has reference to the amount of force (actually the amount of force per unit of strained area) acting to oppose a given amount of strain (percent of deformation). The force of mechanical stress is of a passive nature and involves no active processes or feedback by the system or spring which is exerting the force to oppose distortion. It is attributable primarily to atomic and molecular forces which are balanced when a system is in its equilibrium position. *Physiological stress* is somewhat different. It refers to the combined conditions and processes (within a living body) which are actively attempting to overcome the adverse effects of some agent, frequently an environmental agent. As long as there is no intermingling of physical and biological considerations, the application of these essentially different meanings for the same word poses no problem for the sloppy semanticist. However, in considerations of the problems of weightlessness, the two meanings for the word stress can encroach upon each other. Stress could refer, on the one hand, to the passive mechanical forces of an object which is strained by forces of gravity. On the other hand, the same word could refer to the biological changes which have occurred in the organisms as a result of a change in the gravitational field intensity. Even when reference is only to physiological stress, there might be some confusion as to whether a weightless state would result in a decreased stress as a consequence of the less taxing environment, or in a greater stress as a consequence of the various changes which the body must make in adjusting to an unfamiliar environment. Moreover, in using stress, some biological workers might include not only the reactions of the body but also the actual stressing condition itself, in this case gravity or the lack of gravity.

II. METHODS OF SIMULATING LOW GRAVITY AND WEIGHTLESSNESS

Basically there are four categories of experimental approach whereby one might expect to learn something of the influence of weightlessness. These are: (1) remoteness from heavenly bodies, (2) opposing acceleration, (3) indirect reduction of gravitational effects, and (4) extrapolation of results from exposure to intensified effects of gravity. A selection of certain of the published findings as obtained from these various methods is printed in Table I. The advantages and disadvantages of each approach are tabulated in Table II.

A. Remoteness from Heavenly Bodies

According to existing theory, the only way to achieve a complete and true weightless state would be to position experimental subjects at distances so remote from any body of appreciable mass that no gravitational field will exist. At distances of increasing remoteness from the center of this planet, the Earth's gravity will drop off in accordance with the Inverse Square Law. For instance, if the distance from the center is doubled from the four thousand miles at our planet's surface to four thousand miles above sea level (or a total of eight thousand miles), the gravitational field would be one-fourth of a G. Doubling the separation again would yield a field of one-eighth of a G at twelve thousand miles (sixteen thousand miles from the center).

On the moon, man would experience a field of one-sixth G. On Mercury and Mars, the field would be approximately four-tenths of a G, and on Venus nine-tenths of a G. On the larger heavenly bodies, gravitational fields would exceed the Earth's: 1.2 G on Saturn, 2.2 G on Jupiter, and 28 G at the sun's surface.

As the primary goal of NASA's project Apollo, man is scheduled to arrive on the moon by 1970. There have been many popular descriptions of this project and the project Gemini, which is planned as the immediate series of manned orbital flights. A well-illustrated, highly readable and presumably authentic description of these two projects has recently been prepared by Dr. Hugh L. Dryden (1964), Deputy Director of NASA. A trip to the moon will require man to be either in a weightless or sub-gravity state for approximately one week. Various attempts are being made to predict the effect of various factors (including weightlessness) which man is likely to encounter during this trip. Later, as yet unsolidified plans for trips to our neighboring planets of Venus and Mars will probably require sub-gravity conditions lasting as long as the one and one-half years required for the round trips to these planets. It is hoped that these journeys will be accomplished within the next twenty-five years. The precautions which must be taken in order to prevent adverse effects of exposure to weightlessness during these trips are as yet undecided and will depend in part upon experiments which have thus far not been completed.

B. Opposing Accelerations

At the present time, the closest approach to the simulation of weightlessness is that which is achieved by subjecting experimental objects to physical acceleration of such a direction and magnitude that this artificial inertial field just counterbalances the Earth's gravitational field. With experiments involving artificial satellites, organisms have not been completely removed from the Earth's gravity. The centrifugal field generated by the orbiting of the satellite about the Earth is, however, just equal and opposite to the Earth's gravity. At the center of the satellite, there exists what amounts to a weightless condition.

Many people have correctly stated that the influence of weightlessness cannot be determined until experiments can be performed in space. Yet although this statement is true, its implications are misleading. There is no guarantee that alterations in organisms exposed to a satellite voyage are attributable to weightlessness itself. Only at the center of the satellite are the centrifugal and gravitational fields perfectly balanced. Unless the satellite is spinning upon its own axes fast enough to generate appreciable centrifugal fields, the deviations from zero gravity will be too small to be of probable significance with animal material.

However, the possibility of minute differentials in low gravitational fields might conceivably influence plant material. The Earth's gravity and the satellite's opposing centrifugal field will be in perfect balance only at the satellite's center of mass.

The major disadvantage of satellite experiments is that for some time these satellites will be too small to permit adequately controlled experiments with sufficiently large samples to yield anything more than exploratory results. It is likely that reliable data will be obtained only when controlled conditions can themselves be maintained in the satellite. This would require the centrifugation of controlled subjects in a centrifuge which is itself capable of generating a field of one G. The satellite, therefore, will have to be of a size sufficient that the second-order effects of rotation will themselves not influence interpretation of the control data. The date at which such facilities will be available has not yet been announced.

There have been a number of exploratory experiments which might be interpreted by a careless observer to imply that weightlessness can cause effects at the cellular level. Space travel has been reported to cause mutations with fruit flies (Glembotskiy and Parfenov, 1962). Arsen'yeva et al. (1962) report that histological disorders were observed with mice in the bone marrow and spleen for two days following space flight; there was sticking together of the chromosomes and possibly a disorder of the spindle apparatus of certain cells. Petrukhin (1962) reported that histological observation of the brain, liver, muocardia, spleen, and adrenal glands in mice and guinea pigs yielded evidence of physiological stress. Katzberg (1963) reported faster growth for human cancer cells and tissue culture. None of these experiments described adequate control conditions.

Satellite experiments reveal that man can survive weightlessness for a period of at least four days. Only one human is known to have experienced discomfort (Titov, 1962); whether or not this discomfort was attributable to weightlessness or to other factors (e.g., rotation of the satellite or the excitement of the voyage) is not known. We do know that with the last two Mercury flights the astronauts acquired orthostatic hypotension, which demonstrated itself upon return to the Earth's gravity. In all likelihood, hypotension resulted from weightlessness. One might ask, however, whether this effect is partially attributable to confinement (J. Amer. Med. Assoc., 188(6), pp. adv. 27-33 (May 11, 1964)), the manner in which respiratory gases were applied (Love et al., 1957; Currie and Ullmann, 1961), or to the emotional excitement of returning from a historic and dangerous voyage. Astronauts report that after a few seconds of exposure there is no discomfort for the sensation of weightlessness. Adjustment to the new environment apparently occurs with no dire neurological disorders. Whether or not longer exposure or a broader sampling of subjects would yield such disorders we cannot say. There was one Russian observation of a preliminary nature with a single guinea pig which was interpreted to reflect changes of the central nervous system (Luk'yanova et al., 1962). For several days after return to the Earth's gravity, the animal exhibited a faster and more enhanced vestibular response and an increase in the electrical activity of the muscles of the extremities.

There have been several papers reviewing some of the observations in satellites and ballistic rockets. Henry et al. reviewed the early rocket experiments in 1952, and more recent rocket experiments together with the early Mercury flights in 1962 (Henry et al., 1962). A brief review of early Russian experiments has been published in English (Kousnetzov, 1958). A translation of more recent experiments has just been published (Kas'yan, 1963). Beischer and Fregly (1962) have compiled a tabulation of the various upper atmosphere and space experiments which have been performed with animals and man through the year 1960. Cain (1963) and also White and Berry (1964) have reviewed the various satellite experiments through the next to the last Mercury flight. The results of the last Mercury flight have been described by Catterson et al. (1963). The Russian interpretation of various manned flights has been published in English by Parin (1962). A comparison of the experiments performed in each of the Russian manned flights has been recently tabulated by Carlson (1964).

The Air Force recently announced that it will perform a series of experiments with their MOL or Manned Orbiting Laboratory (Aviation Week and Space Technology, 1963, 1964; Watkins, 1964). In this program, the biomedical aspects of wieghtlessness will be given special attention. Later orbits will build up to as long as six weeks. The total program will last eighteen months. The MOL will not possess facilities which will permit the satisfactory centrifugation of human, control subjects at one G within the MOL. In the early flights, such control studies with smaller organisms are not contemplated. Captain Duane E. Graveline, a member of the MOL Committee at Brooks Air Force Base, has supplied the following additional information in a letter dated April 28, 1964:

> The first programmed MOL flight will be in 1968. The Gemini X capsule will be used . . . as the taxi for launch and deorbit. Once in orbit the two occupants will trans-

fer to the MOL vehicle. It will be a non-rotational vehicle and the programmed flight durations for all six shots will be thirty days.

NASA has announced a series of experiments with lower animals and plants in a series of satellite flights. This series is referred to as the "Biosatellite Program." Some of the details of this series of experiments were released at the recent meeting of the American Association for the Advancement of Science in Cleveland, by Dr. Dale W. Jenkins, Chief of NASA's Environmental Biology Bioscience Programs Division, and by others.

In a letter of March 31, 1964, Dr. G. Dale Smith, Manager, Biosatellite Experiments and Life Support Systems, NASA-Ames Research Center, Moffett Field, gave the following brief description of the Biosatellite Project and a list of experiments currently being considered for space flight:

> The Biosatellite Project consists of six spacecraft. The first is to be launched late in 1965. Flight 1 will consist of General Biology and Radiobiology Experiments and will orbit the earth 3 days. Flight 2 will contain General Biology and Plant Experiments and will orbit for 21 days. Flights 3 and 4 will contain primates for Mammalian Physiology Studies and will orbit for 30 days. All spacecraft will be recoverable. Below are the currently approved experiments:
>
> 1. Plant Morphogenesis under Weightlessness
> 2. Liminal Angle of a Plagiogeotropic Organ under Weightlessness
> 3. The Effect of Weightlessness on Growth of the Wheat Coleoptile
> 4. Nutrition and Growth in Pelomyxa Carolinensis During Weightlessness
> 5. Mutagenic Effectiveness of Known Doses of Gamma Irradiation in Combination with Zero Gravity
> 6. Effect of the Space Environmental Complex on Insect Growth and Development
> 7. Effects of Sub-Gravity on Cellular Phenomena (sea urchin eggs)
> 8. Effects of Sub-Gravity on Cellular Phenomena (frog eggs)
> 9. Mutagenic Effectiveness of Known Doses of Gamma Irradiation in Combination with

Weightlessness on Habrobracon

10. Influence of Zero Gravity on Isolated Human Cells

11. Determination of Influence of "Space Environment" on Mutation Processes Using Controlled Gamma Ray Exposures as a Standard

12. Induction of Lysogenic Bacteria in the Space Environment

13. Effect of Weightlessness on Gross Body Composition of the Rat

14. Effects of Zero-Gravity on Radiation-Induced Damage in Mature Reproductive Cells

15. Possible Effects of Zero-Gravity on Radiation-Induced Somatic Damage

Certain aspects of the instrumentation proposed for work with human cells in the Biosatellite Program have recently appeared in abstract form (Montgomery and Cook, 1964). Another proposal calls for such satellites to carry a pig-tailed monkey for a period of thirty days. Some of the physiological characteristics of this monkey which will be of importance in designing the flight have been recently discussed (Pace *et al.*, 1964).

Many of the results of physiological significance with parabolic (Keplerian) flights of airplanes are difficult to interpret. There are two reasons for this. First, they are of extremely short duration and could not detect changes of the type which would display an elaborate time course. Second, they are generally preceded by a period of simulated high gravity, so that it is difficult to separate the effects of the two different alterations in effective gravitational intensity. Even with such obvious disadvantages, there have been (unsuccessful) attempts to employ this procedure to demonstrate effects at the cellular level (McKinney *et al.*, 1963). Workers at the Air Force School of Aerospace Medicine hope to pursue similar investigations with ciliary motion.

A number of studies concerned with the psychological effects as well as the mechanics of locomotion have been pursued (Simons, 1959; Simons and Gardner, 1960, 1963; Roberts, 1963). Although most of these findings are beyond the scope of the present survey, it is of interest to note that during these flights the relaxed subject will assume a semi-fetal position with his hands raised up in front of his body and his legs raised up part way and bent at the knee. Similar positioning of arms has been reported after awakening from sleep during orbital flight. Subjects in water immersion studies, moreover, assume this same semi-fetal position, and the sensation of both water immersion and these parabolic flights are described as being quite similar. The psychological findings from parabolic flight have been recently described by Hawkins (1963).

In his review, Hawkins calls attention to a preliminary observation of an unexplained increase in isometric measurements of the knee-jerk reflex. He points out that this might be related to the decrease in sensory input to be expected from the various sensory end-organs for stretch in the tendon and in the muscles during weightlessness. He reminds the reader of similarity to the ataxic knee-jerk response of individuals who have experienced sensory denervation. This observation has recently been confirmed with a number of subjects by Captain Robert S. Kellogg (personal communication, 1964) of Wright-Patterson Air Force Base.

English workers (Matthews and Whiteside, 1960; Whiteside, 1961) have previously studied the ankle-jerk reflex arising from stimulation of the Achilles' tendon with subjects in a falling chair. The reflex is absent during the first 0.1 or 0.2 seconds of weightlessness, presumably due to the absence of normal reinforcement arising from muscle weight. Suppression of the reflex did not persist beyond this initial onset of weightlessness.

Captain Kellogg has also pursued studies relative to the magnitude of the counter rolling eye reflex with human subjects during rotation. In prarbolic flights, the magnitude of this reflex decreases as gravitational field intensity increases. Previous studies with centrifugation have shown that the magnitude of this reflex will increase with enhanced gravitational intensity. These findings will be presented at the May meeting of the Aerospace Medical Association (Miller, Graybiel, and Kellogg, 1964).

Another study involving parabolic flights is concerned with the metabolic requirements for human work during weightlessness. This is a joint project between Dr. W. Fedderson (Manned Spacecraft Center, Houston) and Captains Charles Doty and Donald Griggs (Wright-Patterson Air Force Base, Ohio). They are employing the C-131 cargo plane, which is capable of seventeen seconds of zero G, and the C-135 cargo plane, which is capable of twenty-seven seconds of weightlessness. They hope to obtain a better estimate of the oxygen which will be necessary during certain exercises to be performed in NASA's Gemini flight. These exercises will be practices for the rendezvous manipulations necessary in the Apollo flights where a portion of the crew will have to leave the vessel for a trip to the moon and then return. Because additional effort will be necessary to provide the anchoring force which would otherwise be provided by gravitational friction, they anticipate that a greater than normal amount of oxygen will be required. These results will be compared to previous studies performed with subjects at one G, who were suspended in Peter Pan suits (involving suspension by hooks to reduce friction). The metabolic requirements will be measured by means of lithium hydroxide capsules and carbon dioxide sensors. It must be recognized that any information obtained by this procedure (*i.e.*, the Keplerian flight) would at best be a very crude estimate. The very short period of exposure coupled with the previous exposure to high gravity will place the investigators at a severe disadvantage.

C. *Indirect Reduction of Gravitational Effects*

Except during such exertions as the previously mentioned exercises and rendezvous procedures, the absence of gravity would be expected to call upon the individual to exert less energy and force. If various types of low activity regimes have the same physiological effect upon an organism as does the weightless environment itself, then such regimes might serve as a method for predicting effects of weightlessness. Most of these procedures suffer from the drawback that in reducing an individual's work load they are forced to reduce the amount of motion to a level beneath that possible in a weightless environment.

1. *Bed Rest Studies*

The bed-rest approach has the advantage that the individual, by assuming a horizontal position, is called upon to exert less work for the maintenance of posture. At the same time, with the decrease in effective heights of columns of fluid (*e.g.*, blood), there is a decrement in the gravitationally-induced hydrostatic pressures.

Bed rest is probably the oldest form of medical treatment. For this reason, it is somewhat shocking to learn that there has been very little scientific investigation of its effects. Like gravity, it was considered a normal condition, taken for granted, and, therefore, thought not deserving of extensive scientific investigation. Taylor and his co-workers (1945, 1949) are credited with performing the earliest scientific study concerned with the physiological effects of bed rest. Actually there was an earlier study of bed rest performed in Glasgow (Cuthbertson, 1929). But since that study also involved the use of limb immobilization, it will be discussed in a later portion of this section. The Minnesota study involved five conscientious objectors with no controls save for pre-bed-rest and post-bed-rest values for the same subject. They were young men of twenty to thirty-two years of age who were exposed to continual bed rest for a period of three to four weeks. Their caloric intake during bed rest was purposely reduced and adjusted in such a manner as to maintain constant body mass. A nine percent decrease in basal metabolic rate was observed. Although there was no change in resting cardiac output, there was a progressive increase in resting pulse rate with a smaller heart size and stroke volume. At the end of bed rest, subjects displayed the symptoms of hydrostatic hypotension. A nine percent loss in blood volume was reported and attributed to a reduction of the plasma volume. During recovery, the pre-bed-rest degree of mechanical efficiency for work was displayed. However, there was a decrease in the efficiency with which oxygen could be removed from the air in the lungs. A decreased ability of the blood to take up oxygen in the lungs and to remove lactic acid was reported for post-bed-rest exercise.

Although the ability to exert muscular force as measured by hand-grip remained normal, a small loss of nitrogen, indicative of muscle loss, was reported.

All irregularities of function eventually returned to normal after the end of maintained bed rest. Muscular strength and postural coordination recovered within four days. Blood lactate levels following work recovered within two weeks. The capacity for maximum oxygen intake during exercise recovered sometime between sixteen and thirty-six days.

A recent study at Lackland Air Force Base (Brannon *et al.*, 1963) is the only published account (prior to May, 1964) of a bed rest experiment with a sufficiently large and homogeneous sample of men to be considered anything more than a pilot study. It involved the use of thirty male subjects who had just completed a six week period of basic training. Subjects were permitted to sit in bed but were not permitted to leave it during the sixty days of the experiment. The subjects were divided into five different experimental groups, which involved different types and degrees of exercise, including a control group, which was subjected to no special exercise routine. There was, in addition, a control group which performed the official U.S. Air Force physical fitness program involving callisthenics. The study was primarily concerned with predicting the possible adverse effects of prolonged weightlessness upon muscular fitness and with determining exercise programs which might prevent any adverse effects.

The investigators found that there was no decrease of maximum handgrip; however, there were varying degrees of decreased girth of the extremities. It was concluded that very little exercise was necessary in order to maintain muscle integrity in a well-conditioned individual, and that isometric exercise probably would prove adequate to maintain muscle integrity during space trips. Apparently the investigators' considered development of maximum muscular force and muscle size adequate criteria for muscle integrity. The recent finding of Elliott and Thomson (1963) would suggest that a continuation of the work by the Lackland group should also include a more rigorous criterion for muscle integrity, that is, one which would consider the ability of the muscles to perform light work.

Other observations were made with respect to changes in the blood, urine, body weight, pulse, blood pressure, basal metabolic rate, vital capacity, electrocardiographs, visual acuity, reaction time, and radio-graphic density of the skeleton. Of these, save for a decreased body weight in the experimental subjects, no changes were observed. It is interesting to note that no changes were observed in the urine with respect to volume, specific gravity, or calcium content. The details of this data are not described. For this reason, it is not possible to ascertain if the lack of measurable differences was perhaps obscured by scatter in the results or by the procedures employed. At the end of the experiment, dizziness together with pain in some of the weight-bearing muscles and joints was noticed.

One shortcoming of this excellent study is that for many of the experimental findings only qualitative descriptions of conclusions were published. Colonel Brannon (personal communication, 1964) has informed the reviewer that although quantitative measurements were carefully analyzed, other commitments (with respect to available time) will in all likelihood preclude presentation of this data in published form. This is unfortunate. Information concerning the nature of trends and scatter in their data would permit evaluation of compatability with other studies. Moreover, this information would be useful in the design of more advanced studies by other groups.

A continuation of this program should be encouraged. No studies of this nature are presently being pursued by the group at Lackland, however, and their senior investigator, Colonel Earl W. Brannon, will no longer be available to direct this program. He is being transferred in July of this year to Biloxi, Mississippi, where he will become director of the Air Force Hospital.

At Boeing Aircraft in Seattle, attempts to establish exercise programs during bed rest are under way. It is proposed that such exercise be adequate for preventing cardiovascular deconditioning during weightlessness (Grave, personal communication, 1964; Grave *et al.*, 1964). Experiments are being conducted with an unspecified number of subjects subjected to tramboline and isometric exercise. Horizontal subjects are impacted against vertical trambolines alternately at the head and toes at the rate of once per second. Isometric exercise and passive tramboline exercise (*i.e.*, the bed is moved between trambolines without assistance by the subject's motion) are reported to be significantly better than active tramboline exercise in maintaining the ability to exhibit a normal pulse pressure during tilt-table tests. Grave and associates feel that more than one hour per day (possibly one and one-half hours per day) is necessary to prevent deconditioning during an eight day exposure to bed rest.

Another bed rest study has been pursued at Lankenau Hospital. It involved studies with three or four healthy young men of approximately twenty years of age exposed to forty-two days of bed rest. These men (unlike the subjects in the Lackland study) were not permitted to sit up in bed. With the exception of limited observations with only one subject (Di Giovanni and Birkhead, 1964), results of this study have not been found in published articles, but they have appeared in reports and abstracts (Birkhead *et al.*, 1963a,b, 1964). A large number of cardiovascular, respiratory, and exercise tests were performed with the subjects. However, due to the small number of subjects for which results have thus far been reported, most of the findings should be considered of a preliminary nature.

Unlike the combined immobilization-bed rest studies, where there is apparently enough restriction of activity to permit measurable loss of nitrogen in the urine, no such phenomenon could be detected in this study. However, with subjects which were not permitted to sit up (unlike the Lackland group), increased quantities of urinary calcium and phosphorus were measurable.

In a subsequent study, two of the four subjects were permitted to exercise while in bed. At the end of the experiment, these two subjects exhibited essentially normal tolerance to work, but orthostatic intolerance and increased calcium loss were not prevented. A confirmation of this finding with a larger number of subjects would indicate that the muscular exercise (in this case bicycle exercise) is capable of maintaining the subject's ability to do work but that the maintenance of a prone position permits deterioration of the skeleton and loss of gravitational tolerance. On the other hand, eight hours per day of quiet sitting (with an unspecified number of subjects) was reportedly a sufficient gravitational exposure to maintain normal calcium levels in the urine and to prevent orthostatic intolerance. Although orthostatic intolerance was noted, there was, at the same time, no observable increase in hematocrit (unlike the observations of Taylor *et al.*, 1945). On the basis of an observation with only one subject, they report that (as would be expected from the loss of blood volume) orthostatic intolerance was enhanced if dehydration of the body occurred during bed rest (Di Giovanni and Birkhead, 1964). This is cited as being in agreement with previous observations with a single subject by Adolph *et al.* (1947).

Another bed rest study involving a relatively small number of subjects (five or six men) has recently been completed in Houston at the Texas Institute for Rehabilitation and Research by Doctors Fred Vogt, William A. Spencer, and Pauline B. Mack for the NASA manned space flight center. As this study has not yet been published and the report describing the study (although scheduled for completion in February, 1964) has not been released at the time of this writing, the description of this study is based upon a relatively short conversation with Dr. Vogt. In spite of the relatively small sample, he was enthusiastic about the results and felt that a number of physiological tests showed high statistical significance. He did express some reservations about the results of post-bed-rest exercise studies and felt that they might require a larger sample for statistical validation.

One reason for Dr. Vogt's enthusiasm is a new radiographic test for bone density. It is an improvement of one previously reported by Mack *et al.* (1959). The procedure involves relative rather than absolute changes in radiographic density. It supposedly can detect changes in bone density of the order of five percent, whereas older techniques, which are the only ones presently available to other bed rest studies, can detect changes of the order of only ten or twenty percent. (Individuals desiring a copy of the yet unfinished report by the Houston group should direct their requests to: Crew Systems Division, NASA-Manned Spacecraft Center, Houston, Texas.)

The most elaborate of the bed rest studies to date is presently nearing completion in the Air Force School of Aerospace Medicine (SAM) at Brooks Field, Texas. The first two of a series of articles describing these results have appeared in *Aerospace Medicine* (Lamb, 1964; Lamb *et al.*, 1964). More recent findings have appeared only in abstract form (P.B. Miller *et. al.*, 1964). Brief descriptions of the initial design and aims of the program have been published [David, 1964; *J. Amer. Med. Assoc.*, 188(6), pp. adv. 27-33 (May 11, 1964)]. This study is being pursued by Major Perry B. Miller, Dr. Bryce O. Hartman, Lt. Col. Robert L.

Johnson, and Dr. Lawrence E. Lamb. Exposure to bed rest involves a total of four weeks divided into two two-week bouts. Seventy airmen of seventeen to twenty-three years of age are serving as subjects. There are twelve subjects each in one of six different experimental groups. One of the groups serves as a bed-rest control group, and the other groups are exposed to various conditions (*e.g.*, slanting beds, intermittent venous occlusion of the extremities, in-bed exercise, and valsalva respiratory maneuvers), which are being tested as possible procedures for maintaining gravitational tolerance. Various determinations are being performed on the experimental subjects. These determinations include tolerance to various types of centrifugation, blood volume, and cardiac output. They have found that the G suit will increase tolerance of deconditioned subjects to transverse G. This study is an outgrowth of earlier studies with orthostatic hypotension of Air Force personnel which were originally started by Dr. Lamb in 1958 (Lamb, 1959, 1960; Lamb *et al.*, 1960; Lamb and Roman, 1961). The present study was proposed in November of 1961, and implemented in January of 1962.

In a recent conversation, Dr. Lamb pointed out that this study will have several advantages over other previous or existing studies. It will be the first bed rest study involving a large sample. It will be the first study evaluating G suits as a procedure for circumventing the bed-rest-induced hypotension. A large number of determinations will be made with blood, urine, and fecal samples. All of the urine and fecal samples will be preserved so that additional tests can be performed at a later date if the need arises.

Certain phases of the SAM program have been completed. The laboratory phases of the program were scheduled for completion by the first of May. In a recent interview published in the *J. Amer. Med. Assoc.*, Dr. Lamb suggested that the orthostatic hypotension associated with space flights results largely from confinement rather than from weightlessness.

On the basis of a recent semi-popular review (Müller, 1963), one can ascertain that one bed rest study has been pursued for the purposes of weightlessness simulation (presumably with a single, selected subject) in Dortmund, Germany. In this review, Müller points out that during space travel relatively simple isometric exercise of the type advocated by the Lackland group would be adequate for maintaining the ability to perform short periods of maximal work. However, in agreement with the findings of the Minnesota group that the ability for distribution of oxygen to the tissues can be deconditioned by bed rest, and in agreement with the findings by

Elliott and Thomson (1963), he points out that somewhat more elaborate procedures would be necessary to maintain the ability for sustained exercise and work. Müller suggests that thirty seconds of maximal exercise with such devices as bicycle and hand-crank ergometers would provide sufficient stimulus to keep the cardiovascular and respiratory systems properly conditioned. He also points out that exercises necessary to maintain neuromuscular skill would be the hardest to perform during space travel, but, once learned, such skills could be maintained throughout the time of a relatively long space flight. On the other hand, he contends that the efficiency of oxygen supply and lactic acid removal would diminish perceptively with one week of inactivity.

2. *Suspension or Support by Frictionless Devices*

There are a number of different studies being pursued which involve suspending a man by mechanical devices and which tend to reduce the gravitationally-imposed frictional forces, although they do not eliminate the action of gravity upon the subject. Most of these studies are concerned primarily with the mechanical and psychological complications involved when man is required to perform tasks or exert purposeful force (Dzendolet, 1960a,b). In some cases, this will involve the extra muscular effort which must be exerted to replace the gravitational friction. Studies with metabolic requirements, as determined by means of a "Peter-Pan suit," have been briefly discussed in the section pertaining to parabolic flights.

Another approach which might find eventual application to weightlessness studies is the support of subjects in an apparent levitation by means of jets of air. This procedure has been employed at the Royal National Orthopaedic Hospital in London to support pigs for as long as four hours (Scales, 1961) and for people for as long as one and one-half hours (Scales, 1964; personal communication and paper scheduled for presentation May 11th to 12th, International Symposium on Wound Healing, Gif-Sur-Yvette, Paris). Levitation offers certain potential advantages over bed rest, in that it reduces the possibility of bed sores and other results of gravitationally-induced friction which could be encountered during bed rest studies. The technique was developed primarily for use with treatment for burns, and, at the present time, it has not been applied to any investigation of possible effects of weightlessness. This procedure apparently causes no adverse effects or damage to tissue by air pressure or by the cooling of air. Somewhat similar methods of air suspension for people are being pursued at the Bio-Mechanic Center of Wayne State University. But at Wayne the use of air suspension as a means of weightlessness simulation has not been pursued (Herbert R. Lissner, personal communication, 1964).

3. *Cast or Splint Immobilization Combined with Bed Rest*

No recent or existing studies were located which involve the combined effects of bed rest with the application of casts or splints for further immobilization with normal human subjects. Although various observations with people confined to bed due to bone fracture or various diseases have appeared, only two studies with healthy subjects are known. These are the Glasgow studies performed nearly forty years ago and the Cornell studies pursued almost twenty years ago.

One of the principal disadvantages of immobilization as a method of simulating weightlessness is that it imposes a greater reduction in movement than is likely to occur in a weightless state. Moreover, in comparison to the amount of movement possible, there will be a greater development of muscular force. Due to the lack of motion, a greater deterioration of the joints is likely to occur than would actually occur in a weightless state.

The studies in Glasgow (Cuthbertson, 1929) involved ten to fourteen days of immobilization with seven normal subjects of differing ages and sexes. One of the lower limbs was immobilized by means of a splint while the opposite limb was immobilized by tieing it to a sandbag. Each subject acted as his own control and was permitted the same amount of dietary intake during bed rest as was consumed during the control period which preceded the experiment. Although the subjects were propped up in bed, they were asked to avoid all uncessary movement. On the basis of the analysis of food intake, together with that of urinary and fecal output, it was concluded that there was a loss of sulfur, nitrogen, phosphorus, and calcium. This would be indicative of a net catabolism of muscle and bone. There was little change in creatin. Although there was a decrease in the resting metabolic rate, the decrease was very slight, presumably because the patients all were allowed to sit up in bed.

The studies at Cornell (Deitrick *et al.*, 1948; Deitrick, 1948) involved four normal healthy young men who were immobilized from six to seven weeks. They served as their own controls and were permitted to consume the same constant caloric intake preceding, during, and following the immobilization. Immobilization involved a bivalved plaster cast, which extended from the toes to the umbilicus. The subjects remained in the cast throughout immobilization, save for thirty to forty minutes daily during which time they were subjected to ergometer and tilt-table tests and were permitted the use of the bed pan. It has since been reported that only a small amount of exercise is necessary to maintain a large part of one's muscular fitness (Brannon *et al.*, 1963; Müller, 1959; Hislop, 1963). Perhaps more drastic results of deconditioning would have been observed had more continuous immobilization been maintained.

There was a net loss in nitrogen, calcium, phosphorus, sulfur, sodium, and potassium. Increased nitrogen excretion was obvious by the fifth or sixth day of immobilization and attained its maximum level by the second week. The total nitrogen loss amounted to approximately fifty grams per subject. As fracture patients display increased nitrogen excretion within two days and attain the maximum level within six days, the authors concluded that immobilization alone did not account for all the nitrogen loss following trauma or operative procedures. Most of the nitrogen loss occurred in the urine, while the level in the feces was essentially the same as the control level. Although there was no increase in creatin or creatinine excretion, there was a decrease in creatin tolerance, which was interpreted to mean that there was a lowered ability by the muscle to store this substance.

There was a decrease in the ability of the lower limb to exert force by pushing. For that reason, and because of decreased girth of lower limbs, it was concluded that there was a decrease in muscle mass. Sulfur was excreted in the urine in the same proportion to nitrogen as the two elements are known to exist in muscle protoplasm. At the end of immobilization, there was a retention of nitrogen, phosphorus, sulfur, and potassium. This retention persisted for approximately six weeks.

The high calcium excretion occurred in both urinary and fecal samples, starting by the second or third day with the urinary samples. These reached their maximum level during the fourth or fifth week of immobilization. It was double the control level. Total calcium loss was of the order of fifteen grams. They computed one or two percent loss of total calcium. This could not be observed in x-ray examination of the skeleton. With the methods available at that time, it was estimated that at least a ten percent loss of skeletal calcium would be necessary for radiographic detection. The high calcium content of the urine, together with a greater alkalinity, increase in phosphate concentration, and lack of accompanying increase in citric acid concentration was considered conducive to the precipitation of calcium phosphate in the form of kidney stones (Flocks, 1945). In this particular study, moreover, unlike in some of the other hypoactivity studies, there was not the marked increase in urine flow which would have tended to discourage the precipitation of calcium phosphate. Until such time as the nature of the urine concentration and volume during weightlessness is well established, this finding would suggest that astronauts should consume large quantities of water so as to ensure adequate flow to prevent stone formation (Flocks, 1945). If an adequate recovery system is not employed for supplying water from a cycling process or as a by-product from fuel consumption, this could impose an even heavier required payload than would otherwise be anticipated for extended space voyages. At the end of immobilization, there was retention of calcium from the urine. This retention had not been completely stabilized at the end of six weeks of controlled conditions.

A gradual decline in basal metabolic rate occurred, but even with a caloric intake equivalent to the control intake, there was no marked change in body mass. The authors suggest that an increase in fat content was obscured by a decrease in muscle and bone mass.

Orthostatic hypotension occurred. Although a decline in blood volume might have been a contributing factor, the authors suggest that orthostatic hypotension was primarily a result of decreased opposition to venous engorgement in the legs. Raising a person to the vertical position on the tilt table would result in a measurable increase in leg girth. Moreover, wrapping the legs with ace bandages enhanced the subject's tolerance to gravity in a standing position. As measured by Master and Schneider tests, there was a decrease in exercise tolerance. By the end of immobilization, resting pulse rate had increased by four beats per minute and increased by another five during the first three weeks of recovery. More than six weeks were required for the return of normal reclining pulse rate. Exercise tolerance returned in from four to six weeks.

Unlike the results of the Minnesota study and other approaches related to weightlessness, there was no measurable change in heart size or hematocrit.

In a later study, the Cornell group found that by use of an oscillating bed some of the effects of immobilization could be reduced (Whedon *et al.*, 1949). Three of the subjects that were employed in the previous study were exposed to a similar regime of immobilization during a three week exposure in a Sanders bed, which rocked through an excursion of twenty-four degrees every one and three-fourths minutes. The feet moved five degrees above and nineteen degrees below the horizontal. Most of the previously observed effects of immobilization were reduced. The loss of nitrogen and calcium was approximately one-half the fixed-bed level. Unlike the experiments with the fixed bed, which resulted in orthostatic hypotension, there was essentially no loss of tolerance to normal gravity in a vertical position.

The reasons for the lowered deconditioning during this tilting procedure are somewhat obscure. The slight gravitational effect upon the circulatory system would stimulate a better state for the cardiovascular system. Better circulation would occur. In the state of constant disuse of muscle and skeleton, however, it is difficult to comprehend the decreased loss of nitrogen and calcium. The authors suggest that as the bed tilts partial weight-bearing is required.

Dr. G. Donald Whedon, one of the members of the Cornell group and presently Chief, Metabolic Diseases Branch and Director of National Institute of Arthiritis and Metabolic Diseases, stated in a recent letter that he was unaware of subsequent studies of this type with normal human subjects. The present reviewer was unable to locate any such existing studies.

The Cornell group, however, pursued metabolic observations with individuals suffering from poliomyelitis (Whedon and Shorr, 1957). Losses of calcium, phosphate, and nitrogen were of the kind to be expected from this type of immobilization. The oscillating bed proved useful in maintaining cardiovascular conditioning. This treatment demonstrated a small but significant reduction of other metabolic deterioration. Treatment with gonadal steriod hormones did reduce some of the metabolic symptoms of immobilization, a finding which is in agreement with previously reported findings for bones of denervated rats treated with estradiol (Armstrong, Knowlton, and Gouge, 1945).

A more recent study with eight poliomyelitis victims eighteen to forty-seven years of age has been published by Heaney (1962) at Creighton University in Omaha. Rates of calcium turnover were observed by use of the radioactive isotope Ca^{45}. Heaney concluded that, for his subjects, immobilization results in a net loss of bone calcium due to bone catabolism. Anabolism as indicated from rates of calcium resorption was even greater than for a control group of four healthy subjects (thirty-two to sixty-five years of age and presumably not subjected to comparable immobilization). Osteoporosis, however, is known to proceed at faster rates with older subjects. Further studies with more comparable control groups, immobilized healthy men and animals, and young subjects undergoing physical growth could be quite rewarding and could help to clarify Heaney's suggestion that strain does not actually stimulate growth itself but merely discourages calcium catabolism.

An active interest in the problem has been maintained at Omaha. Attempts have been made to measure bone kinetic changes in animal experimental models of immobilized polio patients. At the present time, these animal studies have not advanced to the stage which would warrant conclusions (Heaney, personal communication, 1964).

4. *Partial Immobilization*

There have been a number of experiments which have been concerned only with immobilization of part of the organism. These have been pursued for the most part by investigators who were concerned not primarily with the problems of weightlessness but rather with what might be related problems at the isolated level: decreased motion, decreased muscular force, decreased sensation, and decreased stimulation. The only experiments with normal humans have involved plaster-cast immobilization of the arms. More sophisticated studies with animals have involved not only plaster-cast immobilization but also tenotomy, together with denervation of certain regions of the body.

Although plaster-cast immobilization is among the least satisfactory simulations of weightlessness, it is essentially the only procedure suitable for both man and lower animals, save for certain experiments which have been performed from otherwise healthy human amputees (Ralston, 1953; Sunderland, and Lovorack, 1959).

a. Immobilization of Animals. In animal experimentation, immobilization of a single muscle or limb has been effected not only by means of plaster-cast immobilization but also by means of severing tendons and by various degrees of denervation. All of these methods suffer from a disadvantage in that they reduce the amount of work and motion achieved by one portion of the body to an extent which is greater than in a weightless state. At the same time, there is less influence upon the rest of the body.

Another note of caution is necessary in interpreting any immobilization studies with animals. Any type of restriction is likely to cause a considerable degree of "physiological stress" which would not be likely with a human who appreciated the necessity for the experiment. The struggling of the animal against restriction, moreover, is likely to cause greater internal work by various muscles than would be the case for the same animal exposed to a weightless environment.

b. Effects upon the Nervous System. Although it has been possible to study some nervous phenomena, there have been few reports describing effects of this limited type of immobilization upon the nervous system itself with respect to results from prolonged lack of stimulation of the receptors for stretch in the muscle and tendons. It has been reported that after twenty-eight to seventy-two days of tenotomy of the cat's gastrocnemius stimulation of nerves leading from this muscle will result in a greater than normal monosynaptic response displaying a slightly shorter delay time (Beránek and Hník, 1959). If parallel experiments with sensory denervation could confirm this finding, one might strongly suspect that prolonged exposure to low gravity would result in a lower synaptic threshold. The results with human knee-jerk reflex enhancement during Keplerian flight suggest that there might be even an almost immediate threshold decrement (Hawkins, 1963). Eccles and McIntyre, however, report the opposite results for dorsal roots severed just distal to the dorsal ganglion. Twenty to forty days later, they found a greater delay time and a decreased magnitude of reflex spikes recorded from the nerves leading to the gastrocnemius muscle of cats upon stimulation of the supposedly intact central portion of the dorsal root. Beránek and Hník feel that the discrepancy in results can be attributed to the degeneration of dorsal root fibers. Eccles and McIntyre (1953) noted this degeneration but did not consider it to be of appreciable magnitude.

c. Effects upon Musculature. Any of these immobilization procedures will cause muscle atrophy. Schottelius *et al.* (1954) demonstrated, on the basis of length-tension studies, that tenotomy and plaster-cast immobilization cause the muscle to develop essentially the same type of contraction dynamics. The red muscle fibers are believed to be more closely associated with sustained (as contrasted to phasic) muscle movements than are the white lighter colored fibers. Muscles which contain predominantly red fibers, moreover, are associated with postural reflexes. These muscles are considered to be the antigravity muscles that do the majority of work in supporting against gravitational force (Bourne, 1963). It has recently been reported by McMinn and Vrbová (1962) that such muscles with the rabbit, when tenotomized, demonstrate a faster degeneration than is the case for pale muscle fibers. As this rapid atrophy is not so pronounced if the spinal cord is sectioned at the same time as tenotomy is performed, it has been suggested that part of the atrophy might result indirectly from the effects upon reflexes which are influenced by tenotomy.

There has been a general tendency in studies of hypoactivity to equate constancy of muscle mass or maintenance of maximum contractile force with lack of atrophy. Future studies should place greater emphasis upon analysis in terms of more meaningful considerations, such as contraction dynamics and chemical constituents of muscle.

d. *Human Muscular Changes with Plaster-Cast Immobilization of the Arm.* Immobilization studies with the human forearm confirm that in general reduced muscular force and, to a lesser extent, a decreased muscle mass will occur as a result of restricted muscular movement. This was first reported by the Dortmund group in Germany (Hettinger and Müller, 1953; Hettinger, 1955, as cited by Hislop, 1960, 1963). Employing three subjects immobilized at the elbow but not at the wrists for a one-week period, they noticed that the decrease in maximum force of contraction would occur. The rate of muscular strength loss was reported to be four times as fast as that which would occur with normal subjects at the end of a period of muscle training. They noted, moreover, that the rate at which the muscle regained its strength at the end of immobilization was much faster than the rate of increase with strength in the training of normal active muscle. A relatively small amount of exercise was reported necessary to prevent atrophy of the immobilized muscle. A contraction for ten seconds per day of one-fifth of the maximal force which could be exerted by forearms reportedly prevented atrophy of the ability to exert muscular force. Since this investigation was with only three (presumably selected) subjects, and since it yielded somewhat scattered results, it can be considered little more than a pilot study.

Hislop (1963), while at the State University of Iowa, performed a somewhat similar study. However, she used twenty-one subjects, and hers is probably the only human study with plaster-cast immobilization involving enough data to yield good quantitative measurements of atrophy rate. The subjects were healthy, sedentary young men. The right arm was enclosed in a bivalved cast, which immobilized all of the limb except the fingers and the shoulder. The arm was held at an angle of eighty degrees at the elbow. Measurements were performed over a period of twenty-eight days. The subjects were divided into various experimental groups which performed varying degrees of isometric work.

Hislop's investigation involved testing the strength of the flexors of the forearm. The maximum amount of force which could be exerted on a grip dynamometer was used as the criterion for strength. Of the seven subjects who performed no exercise (save for weekly testing of grip-strength throughout the twenty-eight days), there was a thirty percent loss of strength. During the first week of immobilization, there was a twelve percent loss in strength. This is a slower rate of loss than the somewhat less precise values of the Dortmund group. With a maximal exercise of six seconds per day, Hislop's subjects lost only ten percent of their strength throughout the twenty-eight days; and with a two-thirds maximal exercise for six seconds per day, there was a fifteen percent loss in strength. She concluded, as did the Dortmund group and as did the Lackland group with bed rest (Brannon *et al.*, 1963), that a very small amount of isometric exercise is necessary during inactivity to maintain muscle strength. As any measurable changes in arm girth were less even than those in muscle strength, she thought that the changes involved factors of training and learning at the level of higher nervous centers rather than true physical changes to the muscle. It should be emphasized that Hislop's conclusions were based on the assumption that ability for exertion of maximum force (without a consideration of the ability for muscular work) is an adequate criterion for muscular strength.

e. Effects of Tenotomy upon Animal Musculature. Tenotomy has certain similarities to the condition in the weightless state. Once the tendon is cut, the muscle will be able to contract as it would in a weightless state, but since it is no longer pulling against the attachment, the muscle will encounter little gravitational force to oppose its contraction. With the reduced tension, there will be less sensation of stretch arising from the sensory end-organs in the tendon and in the muscle. In growing rats, a slower development is reported for tenotomized muscles (Zelená, 1963). There is an atrophy in size and decrease in ability to exert force with tenotomized muscles of mature rats (Schottelius *et al.*, 1954). With limbs immobilized by means of a plaster cast, there is even some atrophy of muscles of the controlateral limb (Schottelius *et al.*, 1954). The atrophy appears to be related to the fact that the muscle will receive stimuli for contraction less frequently; and when it does contract, the muscle will be shortened already, so that it is not able to perform active shortening during the process of contraction (Eccles, 1941, 1944; Wehrmacher *et al.*, 1945).

f. Denervation of Animals' Musculature. With vertebrates, complete denervation of muscles can be achieved simply by removing all the nerves innervating a muscle or limb. If it is desired to achieve immobilization resulting in no voluntary movement by the muscle while its sense organs are still able to detect the effects of stretch, motor denervation can be achieved by severing the ventral roots of nerves as they leave the spinal cord. On the other hand, if it is desired to remove only the sensations of stretch (such as might occur as the result of weight or other gravitationally-induced force), sensory denervation can be achieved by means of severing the dorsal roots of the spinal nerves as they enter the spinal cord. The effect of denervation upon skeletal muscle has been reviewed elsewhere (Tower, 1939; Hines and Thomson, 1956). A recent symposium on this subject has also been published (Gutman, 1962).

Denervation causes a more pronounced atrophy of the muscle's ability to exert force than it does upon its size (Hines and Thomson, 1956). Electrical stimulation can reduce the rate of atrophy. Muscles of the hind limb of the cat with combined tenotomy and sensory denervation displayed a pronounced atrophy of force of ability for exerting maximum muscular force even when the muscle had been exercised by means of stimulating motor nerves (Eccles, 1944). It is interesting to note, however, that only a few seconds of exercise per day were as effective in maintaining this ability to exert force as was exercise for as long as two hours per day. Eccles believed that the atrophy was a result of muscle shortening as a result of no tendon attachment. Yet later studies would indicate not that the shortening itself caused the atrophy but that the stimulated muscle already in a shortened state was unable to perform the same degree of exercise as would an initially taut or stretched muscle (Wehrmacher *et al.*, 1945).

Considerable confusion with respect to the influence of immobilization, denervation, or other types of hypoactivity upon the atrophy of muscle might arise from the criteria for atrophy. Most criteria are based either upon the ability of the muscle to exert force during maximum stimulation (or motivation) or upon the mass of the muscle itself. These criteria would be most useful for weight lifting and for esthetic appearance of the physique. The fact is that such criteria overlook considerations of the muscles' ability to shorten and to do useful work. The concept that a small amount of isometric contraction by various muscle groups will be adequate in the maintenance of the muscular system should be examined in the light of the recent work by Elliott and Thomson (1963) at the State University of Iowa concerned with the denervated gastrocnemius muscle of the rat. In addition to the control animals which were not denervated and a set of experimental animals which were not exercised, two sets of experimental animals were exercised by means of direct electrical stimulation of the muscle. With one group, the muscles were exercised by periods of isometric exercise throughout denervation; with another group, they were exercised by means of isotonic exercise which permitted an actual shortening. The animals were sacrificed, and the dynamics of their change of length and tension throughout contraction against different loads and under different conditions of imposed length were measured and analyzed by means of Hill's Equation for Muscle Shortening. Elliott and Thomson studied the ability of the various experimental muscles to exert maximum (isometric tetanus) tension, the rate at which shortening could occur, the amount of shortening which was possible, and the ability to perform work during isotonic contraction. As would be expected, the control muscles performed best in all tests, while the denervated muscles which were not exercised showed the least performance. However, although the isometrically exercised muscles outperformed the isotonically exercised muscles with respect to maximum developed tension and rate of shortening, the isotonically exercised muscles performed best with respect to the amount of shortening which they could achieve and the amount of work which they could perform during isotonic contraction.

g. Immobilization of the Respiratory Muscles. The respiratory diaphragm is one muscle which might actually suffer some degree of direct immobilization as a result of weightlessness. For most of the other muscles, the analogy of immobilization to weightlessness depends upon the extent to which lack of gravitational opposition to motion will simulate the effects of decreased activity. During respiration, the absence of the gravitational assistance in pulling down the abdominal viscera might tend to immobilize the diaphragm. This might result either in greater work to oppose immobilization or in less work under conditions of sufficient immobilization. The likelihood of decreased diaphragmatic work would be enhanced if prolonged weightlessness results in a decreased metabolic requirement for oxygen and therefore for respiratory activity.

The unique nature of atrophy displayed by the diaphragm was investigated at the Sate University of Iowa. When denervation of the diaphragm is accomplished by removal of the phrenic nerve in the neck of rats, an atrophy of the diaphragm ensues (Hines and Thomson, 1956). Although most motor denervated muscles exhibit an exponential rate of decay with an essentially constant decay coefficient for different skeletal muscles from the same animal, the diaphragm exhibits a slower exponential rate than do most of the other skeletal muscles. Thomson (1955) found that within seven days of denervation the rat diaphragm showed no significant loss in dry weight but that it did show an increase in water content with a marked loss of creatine. After seventy days, there was a decrease both in the wet and dry weights of denervated diaphragms. A somewhat similar loss of dry mass and gain of water content has been observed in preliminary studies with mice returned to normal gravity after developing in high centrifugal fields (Wunder and Lutherer, 1964).

With children suffering from tuberculosis and subjected to chronic bed rest, flattening of the chest occurs as a result of loss of bone structure by the ribs and the weight of the viscera acting to immobilize the ribs (Stevenson, 1952). This condition is supposed to decrease the ratio of intercostal to diaphragmatic breathing. Perhaps that ratio would be reversed during visceral weightlessness.

h. Effects upon Bone. For at least a century, it has been generally supposed that the growth of bone, particularly with respect to thickness but not necessarily with respect to growth in length, can be stimulated by moderate stress. It is not unreasonable to assume that the reduction of either the forces of weight or the forces of muscular contraction in a weightless state would result in a subnormal stimulus for both bone growth and maintenance of bone size (as reviewed by Thompson, 1942, pp. 958-1025; and Sissons, 1956). There has been little experimental verification of this suspicion and some doubt as to its validity (Heaney, 1962). There appears to be little doubt that net loss of skeletal calcium and bone mass accompany immobilization.

That immobilization by means of denervation of the foreleg of dogs can cause atrophy of bones was demonstrated in the early part of this century (Howell, 1917; Allison and Brooks, 1921). Similar results were obtained either by plaster-cast immobilization or by removal of a portion of the humerus bone. In either instance, there developed bones of less than normal mass. The principal effect was not upon bone length but upon bone thickness. The shafts were thinner and flatter and displayed thinner cortices, less mineral content, and lower density to x-rays. The suspicion that such changes might accompany low gravity are substantiated by the contrasting results which are sometimes obtained with the bones of mice subjected to 4 G (Wunder *et al.*, 1960a) and to 2 G (Captain Duane Graveline, personal communication, 1964): greater mass, greater roundness of the shaft, and greater radiographic density. Certain of these findings also have been confirmed for centrifuged chickens (Smith and Kelly, 1963). At the same time, sufficiently high centrifugal fields cause slower growth of mouse femurs (Wunder and Lutherer, 1964, and unpublished results). Slower growth at high centrifugal fields presumably is the result of gravitationally-imposed immobilization. The effect of low gravity upon bone atrophy and development should depend upon the net result of greater freedom of motion balanced against lower forces opposing motion.

A more recent study with the heel bones of tenotomized and cast immobilized rabbits has been described by Geiser and Trueta (1958) at Oxford. Their paper is frequently cited in predicting the possible effects of weightlessness upon the skeleton. Trueta has been concerned with the influence of gravity upon the skeleton for the past ten years and is continuing to pursue studies of its influence.

Geiser and Trueta base their report on the results of studies with forty animals. A reduced radiographic density of the calcaneum was observable after one week and progressed to the end of the experiment, which continued over a period of eighty-nine days. Accompanying this was an increased vascularity of the bone and what appeared upon histological examination to be an abnormal number of osteoclast cells. Essentially the same results were obtained whether the animals were immobilized by means of tenotomy or by means of splints. They reported a preliminary study (with two animals) in which the atrophic effects of splint-immobilization on animals could be reduced by means of electrical stimulation of the calf muscles. Their paper was essentially a descriptive rather than a quantitative analysis. However, they reported consistent results for a number of animals, and the photographs which accompany their article, if representative, are quite convincing even to a novice.

Certain aspects of this investigation were continued by DuBois and Geiser (1957) in Berne. Immobilized tibial bones of growing rabbits demonstrated a faster closing of the distal epiphysial plates. To attribute this change in rate to a possible simulation of weightlessness, however, would be most premature. [Similar results are reported for high gravity as simulated by chronic centrifugation of rats at 5 G (Vrabiesco *et al.*, 1964).†] Following tenotomy, the tibias of two of DuBois's and Geiser's experimental rabbits grew to a greater length. The thickness of these bones (in agreement with expectations from lower mechanical stress and the opposite findings with chronically centrifuged mouse femurs, Wunder *et al.*, 1960) was less, however, than that for the control bones.

A study employing the methods of Geiser and Trueta, but one involving a more quantitative interpretation of the results, would be valuable. Perhaps it would also be possible to immobilize the limbs and to then apply various degrees of tension upon the severed tendons in an attempt to obtain relationships between the response of the bone and the degree of applied force or lack of force. It might also be desirable to perform periodic quantitative measurements of the bones' radiographic density as the experiment proceeds. Methods are available which are reported to be quite precise and which do not require termination of the animal (Mack *et al.*, 1959). Studies of isotopically labelled calcium turnover using methods employed by Heaney (1962) would also be appropriate.

†As the cages employed during centrifugation of these rats were quite small, symptoms of gravitationally-imposed weightlessness were more likely than in centrifugation studies employing relatively larger cages.

Thornton and Carlson (1963) at the University of Kentucky have recently reported some chemical determinations performed with cells removed from the tibiae of rats which had been immobilized by means of casts for a period of one or two weeks. Although there was not a decrease in bone weight until the end of the second week, a marked decrease in cell nitrogen was measurable within one week after the onset of immobilization and was interpreted to indicate either a decrease of cell numbers or a change in cell type. An increased glucose utilization per miligram of cellular material was noted. It was suggested that this might mean either that there was greater activity of the remaining cells or that more glucose was utilized due to a deficiency of other energy-forming substances. An increased level of bone citric acid and increased output of lactic acid by incubating bone tissue was cited as evidence for the possibility that bone atrophy resulting from disuse was mediated through the parathyroid gland.

i. Joints. Immobilization is known to cause stiffness or pain in the joints of normal men exposed to bed rest (Brannon *et al.*, 1963) or to plaster-cast immobilization (Deitrick *et al.*, 1948).

Recently there have been some attempts to relate the joint stiffness to changes in the connective tissue. It is known (at least in studies with rabbits) that when immobilization is effected by denervation, in spite of massive tissue atrophy, synthesis of collagen and polysaccharides does continue, although at a decreased rate (Brooke and Slack, 1959). There is some thought (Peacock, 1963) that stiffness at the joints could result from the pattern of collagen formation which accompanies immobilization. On the other hand, Akeson (personal communication, 1964; Akeson, 1961; Akeson *et al.*, 1958) feels that the rate of collagen turnover is too slow to account for joint stiffness and suggests that it is more closely related to a decrease in mucopolysaccharides (which otherwise would serve as a lubricant or buffer between the layers of collagen) and the change in molecular bonding between adjacent collagen bundles (which would accompany the observed decrease in the water concentration of immobilized connective tissue). Akeson's studies have been performed with dogs, the hind extremities of which were immobilized at the knee by means of a threaded wire, which did not penetrate the skin at the knee but rather was drilled to the mid-shaft of the tibia and femur. Akeson noted that this does cause the connective tissue of the knee to lose a significant amount of mucopolysaccharide. He is continuing studies of the chemical composition of immobilized connective tissue. At the present time, he is unable to say whether the changes which he observes can be attributed to the absence of motion or to the absence of mechanical stress.

5. *Recommendations Concerning the Use of Immobilization as a Simulation of Weightlessness*

There are a number of arguments against the use of immobilization studies for predicting effects of weightlessness. The primary objection, of course, is that weightlessness would reduce the amount of work which an individual is likely to perform without necessarily reducing the amount of motion, whereas the primary effect of immobilization would be the reduction of motion. The evidence of Elliott and Thomson (1963) that immobilized muscles subjected to isometric exercise display changes different from those for muscles subjected to a condition which is believed to be more comparable to weightlessness (*i.e.*, isotonic exercise) has been cited. The lack of motion during immobilization would, moreover, result in less muscular pumping of blood than probably would be permitted during weightlessness. Unless extreme care is exerted in the interpretation of future satellite experiments with weightless men or animals, it is quite likely that any similarity between these results and those with immobilization might be interpreted as the result of weightlessness. Actually many changes could result from the immobilization imposed by space restrictions in the satellite. Investigators who have performed other types of weightlessness simulation, such as bed rest, report that there are difficulties associated in keeping the subjects contented during hypoactivity and that they believe that casts or splints would serve only to accentuate this difficulty (Brannon, personal communication, 1964). This degree of restraint might unduly excite or "physiologically stress" the subject. Deitrick *et al.* (1948) reported that in their immobilization studies it was necessary to remove the subjects from the cast for approximately forty minutes per day. A requirement for continuous maintenance within the cast would pose problems with respect to sanitation and enhance the possibility of body sores which would be a source of non-weightless "stress."

As with other simulations based upon low activity, immobilization does not correct for the action of gravity within the subject's body. If combined with recumbency, however, many of the gravitational influences can be appreciably reduced. On the other hand, the natural position of an individual in the weightless state apparently is more of a semi-fetal than of a recumbent nature. Such observations are discussed in the portion of this section which describes studies performed during Keplerian flights (see page 20).

There are certain arguments which favor the use of immobilization in studies basic to manned space travel. These arguments involve problems of direct immobilization rather than problems of weightlessness itself. Many of the symptoms associated with bed-rest inactivity will present themselves more rapidly during the more drastic immobilization effected by plaster casts. In certain respects, immobilization imposes a more drastic decrease in the work load than would be occasioned during weightlessness itself. If the symptoms of weightlessness will be primarily a result of decreased work rather than decreased motion, then immobilization might exaggerate the effects of weightlessness and indicate an upper limit of the results to be expected. In addition, immobilization would, as was previously indicated, be likely to approximate the conditions of early trips in small crowded vehicles. It would, therefore, yield information which would be needed even though it is not information basic to the biological problems of weightlessness. Plaster-cast immobilization is one technique which can be employed with both man and lower animals. It would permit a number of pilot studies which could first be performed in a more efficient manner with lower animals. If a very large study is to be pursued which would compare the effects of various types and degrees of hypoactivity, plaster cast immobilization would offer one more parameter. Finally, very little is known about the normal, physiological effects of immobilization. Even if this knowledge is not directly applicable to space travel itself, an extensive investigation of all phases of low activity might find wider applicability if considerations of immobilization were included as well. This information would be most useful to people concerned with the problems of rehabilitation.

Studies of immobilization with lower animals should be encouraged. One should realize, however, that the results of such studies may not necessarily contribute greatly to the problem of weightlessness itself. Extreme care must be taken to avoid concluding that the results of immobilization with animals either on Earth or in space capsules are necessarily related to the effects of weightlessness itself. So as to avoid the effects of immobilization which are not directly attributable to a similarity to a weightless condition, it would be wise to couple such studies with other types of weightlessness simulation. These other types should not have the same shortcomings as immobilization. Animal studies would be most beneficial if they proposed to obtain basic information for use in designing cast-immobilization experiments with human subjects. One should also remember that if the primary purpose of the immobilization is simulation of weightlessness, then tenotomy rather than the use of casts and splints probably comes closer to effecting the desired condition. Studies with tenotomy of one muscle should be designed so that not only the effects upon the tenotomized muscle itself can be observed. The effects of altered reflexes upon other muscles or groups of muscles should also be observed. In most instances, immobilization studies with animals could be most effectively pursued at universities or related scientific establishments where there are already in existence established programs and investigators experienced in neuromuscular research upon animals.

It is recommended that immobilization studies with men as subjects be pursued only if a number of procedures and precautions are satisfied. The primary aim of such studies should be to gain a more basic knowledge about the deconditioning which results from hypoactivity itself rather than that which is expected to result from weightlessness. If the study is to bear any relationship to the problem of weightlessness, it should be coupled with other studies of hypoactivity and weightlessness at the same time and place. Essentially the same population of subjects would be employed in the one large well-coordinated program. The requirement for a large uniform population of available healthy subjects probably would necessitate that such a study be pursued at or in cooperation with a military base. If the study is to include the effects of various age groups, however, some studies at another institution (*e.g.*, a prison) might be appropriate. Before studies are initiated with human subjects, exhaustive investigation of immobilization with large samples of various animals should be pursued by well-qualified investigators in order to indicate all the potential dangers and avenues of investigation with a subject so precious as the human being. Lack of previous animal work with immersion and bed rest is almost inescapable for pilot studies with humans. Such a lack nonetheless can be avoided in immobilization studies. So that quantitative relationships may be obtained, it is highly desirable that casts of various degrees of stiffness and flexibility be employed with various experimental groups. Naturally it is absolutely essential that the work with human subjects be pursued under the direct supervision (or at least with the constant presence) of medically qualified investigators. These physicians should be familiar with all the previous work pursued at simulated high and low gravity with men and animals. A well-planned program would also require the active and close participation by well-qualified scientists who are familiar with the physical as well as the biological problems of weightlessness. Finally and above all else, let it be repeated once more that extreme caution and conservativeness must be exercised at all times before suggesting that any of the results from immobilization studies are necessarily those which would be expected to derive from a truly weightless condition!

6. *Buoyant Support*

Water immersion of human subjects has several advantages as a method of weightlessness simulation. It reduces the force and work requirements for slow body movements, and it does so without reducing the degree of freedom so drastically as either immobilization or bed rest. The effect of gravitationally-induced pressures in columns of fluid are negated, moreover, due to the fact that they are balanced by the same columns on the outside of the body. At first thought, one might suppose that the requirement for slow motion in face of the greater viscosity of water (as opposed to air) might also tend to impose greater immobilization than occurs in a weightless environment. However, it would seem that, at least in the studies with Keplerian trajectories in airplanes, the experienced subject will execute only slow cautious movements when weightless. Although the amount of resisting force might be different in the two environments, the total amount of motion would be at least qualitatively if not quantitatively similar. The two primary objections to water immersion are, first, that water serves as an unnatural environment from the point of view of temperature exchange and, second, that the type of respiration which either is against a negative pressure or through a series of valves and artificial airways in a mask can induce artifacts which might exaggerate the degree of increased urinary activity to be observed.

It long has been suspected that organisms suspended in water would experience a lower rate of metabolism and heart rate. Although some of the early experiments confirm that this occurs even after a short period of immersion, certain of these findings can be attributed rather to the effects of the water temperature than to the buoyancy itself (Bazette *et al.*, 1924; Goff *et al.*, 1956).

In 1961, two different groups in this country published the results of studies of prolonged immersion. These were the studies by the Air Force groups at the School of Aerospace Medicine and at the Wright-Patterson Air Force Base, and the studies pursued at the Navy School of Aviation Medicine at Pensacola. In both of these studies (as has been the case with essentially all subsequently published immersion studies), the experimental subject served as his own control without an additional control group.

Graveline's study (Graveline *et al.*, 1961) involved immersion of a single subject (Graveline himself at the School of Aerospace Medicine at Brooks Field). Studies of centrifuge tolerance followed (eleven hours later at Wright-Patterson Field) the seven days of immersion. Graveline was positioned in a semi-reclining posture and was immersed to neck level. This is the longest reported prolonged experimental exposure of a subject. No effects were observed during the study which would predict major difficulties during actual weightlessness. There were definite indications, however, of a debilitation which would be troublesome after return to a gravitational environment. A number of the preliminary findings from this study have since been confirmed for shorter periods of immersion with larger and more reliable numbers of subjects. Although there was a slight reduction in the systolic and diastolic blood pressures, the pulse pressure was unchanged during immersion. There was a reduced caloric intake of food, and there was an increased volume rate of urination. However, as the enhanced diuresis might have been attributable to the negative pressure breathing (which would occur during submersion to neck level and therefore stimulate volume receptors in the thorax or auricle much the same way as to be encountered with an enhanced venus return expected during weightlessness), these studies were later repeated with five subjects exposed to six hours of immersion with compensated respiratory pressure (Graveline and Jackson, 1962; Graveline and McCally, 1962). The increased urine volume was accompanied by an increased thirst and probably by a decreased plasma volume (as reflected by a somewhat greater hematocrit). The increased hematocrit, which is actually decreased during the first few minutes of immersion, has been confirmed by McCallly (1964) for periods of immersion lasting several hours. A decreased urinary excretion of norepinephrine was also observed and has since been confirmed for six subjects who were completely immersed (McCally and Graveline, 1963a; Goodall *et al.*, 1964). A calcium loss was noted. This was not reflected by an increased calcium concentration in the urine but by a reduced calcium intake in the diet, which was not compensated for by a reduction in the urine. There was no change in tolerance (as measured by blackout point) to high centrifugal fields for the subject in the recumbent position. Changes in heart rate and subjective effects did, however, show an altered tolerance. A subsequent study with the Navy centrifuge at Johnsville, Pennsylvania, indicated that immediate centrifugation following immersion of experienced divers causes a slight decrease in tolerance (Benson, *et al.*, 1962).

In Graveline's initial study, a decreased tolerance to normal gravity in the standing or vertical position was noted and has since been confirmed in a number of weightlessness studies. There was every indication of orthostatic hypotension, which would be compatible with the decreased blood volume associated with enhanced urination and with the postulated decrease in production or release of norepinephrine (permitting a greater distention of the veins and a decrease of peripheral resistance). Graveline (1962) has since found that the application during immersion of a "physiologically stressing" condition could eliminate orthostatic hypotension following six hours of water immersion (at least with the one type of "stress" studied). The "stress" condition involved simultaneous application of tourniquets on each of the four extremities for one out of every two minutes at sufficient pressure to obstruct venous return throughout immersion of five subjects.

In his original study, Graveline noted a decreased requirement for sleep, which since has been investigated by the Air Force group with more subjects (Graveline and McCally, 1962). There evidentally is some confusion as to whether or not immersion will actually reduce the sleep requirement: with certain subjects, Graybiel and Clark (1961) reported the opposite results.

The 1961 study at Pensacola (Graybiel and Clark, 1961) involved two weeks of immersion in isotonic saline for ten hours per day with bed rest during the remaining time. The study confirmed Gaveline's finding or orthostatic hypotension, but, as Graveline indicated, the deconditioning of the voluntary muscular system was not so pronounced as the deconditioning of the cardiovascular system. Graybiel and Clark suggested that the small amount of work required to climb in and out of the tank each day was perhaps sufficient to maintain the skeletal muscles throughout the experiment.

At the present time, most of the immersion research concerned with the physiological aspects of weightlessness is being pursued by Air Force personnel either at the School of Aerospace Medicine at Brooks Field, Texas, or at the Wright-Patterson Air Force Base in Ohio. Both groups are relatively small and consist of people who have been actively concerned with problems of weightlessness for no more than two years. The laboratory at Wright-Patterson originally was organized by Captain Duane Graveline after preliminary studies with himself at the School of Aerospace Medicine. He was the principal investigator at this laboratory from July of 1960, until July of 1962. Captain Graveline has returned to the School of Aerospace Medicine, where he is presently not actively participating in laboratory investigations but is pursuing an analysis of foreign research in space medicine. Dr. Michael McCally had pursued investigations in association with Captain Graveline at Wright-Patterson until 1962. He was principal director of that immersion facility until he left the service in 1963. At the present time (May, 1964), he is a civilian serving a residency in obstetrics at Yale University. He expects to return to Wright-Patterson this summer. The Wright-Patterson laboratory is currently under the direction of Captain Jack Goldman, who anticipates returning to civilian life in the near future. At that time, he probably will be replaced by another Air Force medical officer, presumably a cardiologist.

New investigations at the School of Aerospace Medicine have only recently been initiated. These studies are being conducted by Captain Daniel Trophy, who will employ a new immersion tank. This tank was recently installed (presumably in March of 1964) and is of a design similar to the one which has been in operation at Wright-Patterson. The tank at the School of Aerospace Medicine will also be employed by Captain Noel Hunt, III, who is presently investigating certain aspects of possible diuresis artifacts associated with the type of breathing which is accomplished during immersion.

The use of the aqualung can create a compensated pressure and eliminate some of the causes of a possible diuresis artifact. The nature of the breathing masks, however, might in itself cause certain artifacts. Love *et al.* (1957) in England, reported that pulsations as great as ±20 mm of Mercury could cause a diuresis. Although the pulsations which occur with the masks employed in the immersion studies are of the order of only 4mm of water, Dr. Hunt is attempting to determine whether or not an artifact could arise from pressure fluctuations of this magnitude. In a recent conversation, Dr. Hunt reported that he has thus far been unable to confirm the results of Love *et al.* (1957). Dr. Hunt is also attempting to investigate the implications of the reported effects of enhanced resistance and greater carbon dioxide upon diuresis, which have been reported with respiration through a mask (Curie and Ullmann, 1961). Dr. Hunt stated that his findings with dehydrated subjects do not confirm the diuresis reported by Curie and Ullmann.

Dr. Hunt is also investigating certain other aspects of the diuresis to be anticipated during weightlessness. This diuresis would be expected to result from reflexes arising from the volume receptors of the left atrium. Inhibition of antidiuretic hormone (ADH) release as a result of greater auricular volume during weightlessness or similar conditions is accepted as a major factor in influencing the blood volume for these conditions (as reviewed by Pearce, 1961; Gauer and Henry, 1963). The influence of reflexes arising from these volume receptors upon salt excretion by the kidney is a more open question (Davis, 1962; Farrell and Taylor, 1962). Graveline and McCally (1962) obtained an increased salt output only indirectly as a result of the increased volume rate of water excretion. Dr. Hunt is presently attempting to determine if there would be a more direct effect of weightlessness or immersion upon the rate of salt excretion.

Dr. Hunt is also preparing a study intended to compare the changes of blood flow, arterial pressure, peripheral resistance, and venus tone, under conditions of immersion to neck level and under conditions of bed rest. The study will involve the use of the ear densitometer and closed segment venometer studies. The bed-rest conditions will be the conditions for the control subjects. As immersion exerts a more drastic effect in negating the gravitationally-induced balooning of veins, he hopes to couple this investigation with an examination of the changes in venous tone.

Another aspect of submersion studies has been the attempts to maintain cardiovascular adaptability by means of physiologic stress. This is similar to the approach of Whedon *et al.* (1949) with immobilization studies where gravitational stress was reintroduced by rocking in an oscillating bed. The first such approach during immersion experiments was the previously mentioned use of pressure cuffs (Graveline, 1962). This is a relatively simple procedure which might be feasible in space flight. Presently related lines of approach are being continued at both Air Force installations in the hope of finding other types of "physiologic stress" appropriate for maintaining cardiovascular conditioning.

Dr. Goldman has noticed that temperatures above 26° C (neutral body temperature) cause a decreased tolerance during tilt-table studies of adaptability. Most immersion studies are performed with the immersion fluid at approximately 33° or 34° C. Goldman is currently looking into the possibility that the bath temperature itself is a factor in changing the metabolism of noradrenalin in subjects. He is studying the noradrenalin level of individuals exposed to various temperature conditions. Eventually he hopes to arrive at some quantitative relationship between degree of various types of "physiologic stress" and ability to maintain desired noradrenalin levels. When the reviewer visited his laboratory in February of this year, Goldman was investigating the noradrenalin metabolism in submerged subjects. He hoped to administer various isotopically labelled precursors of noradrenalin and follow their incorporation into the hormone as a function of time.

Dr. Goldman is also investigating two other aspects of immersion. In collaboration with Dr. Raymond Murray of the University of Indiana and of Wright-Patterson Air Force Base, he intends to pursue certain cardiovascular studies, such as cardiac output. Dr. Goldman is attempting, moreover, to improve the nature of the immersion suit so as to eliminate certain artifacts associated with such discomfort as pinching. In February, he was preparing to test an immersion suit prepared from a new material (Hellenka, a two-way stretch fabric supplied by the David Clark Company of Worcester, Massachusetts).

Dr. Trophy's studies will be parallel or similar to some of Dr. Goldman's work with "physiologic stress." He hopes to study adrenalin and noradrenalin excretion responses to tilting before and after immersion. The results will be compared to results for control subjects who will have rested outside of water. Using the same subjects, he hopes to measure blood volume change. After providing some parameter of deconditioning in the above manner, he plans to evaluate various conditions of stress, such as low temperatures and inhalation of carbon dioxide in preventing deconditioning.

7. *Tumbling Devices*

Most of the methods whereby the effects of gravity are reduced without actually removing the field involve external support or reduction of external work of the organism, so that the various displacements and requirements of work to overcome gravitational forces can be reduced. Those approaches would not account for the internal displacements or requirements for internal work which must be performed in opposition to gravity and which arise due to the lack of buoyancy for interaction between materials of varying densities, such as the otolith particles in the utricle of the inner ear or air in such places as the lungs. In such instances, tumbling organisms at appropriate speeds with the axis of tumbling or rotation at right angles to the Earth's gravitational vector can reduce the effect of gravity. It is necessary that the rate of rotation be fast enough so as to prevent net settling or bending of materials in any direction. At the same time, rotation should be slow enough so as to generate no marked centrifugal field. There is always the difficulty that the optimum rate of rotation for one system in the organism (*e.g.*, the otoliths in the inner ear) is different from that for another system (*e.g.*, the lungs). Moreover, in order to reduce the gravitational field, an organism might be required to be restricted to the center of rotation in such a manner as to cause unnatural immobilization.

Tumbling probably is the oldest method of weightlessness simulation. It has been employed by botanists for almost one hundred years (Sachs, 1872). A device of this type is somewhat more conducive to work with plants than with animals. Since plants are relatively immobile, the problems of restricting their locus to the center of the axis of rotation is markedly simplified. At the present time, individuals hoping to simulate weightlessness by means of immobilization should study the findings with tumbled plants. Here are organisms that even under ordinary conditions in the Earth's gravity are more inactive than an immobilized animal. Nonetheless the virtually immobile plants often can demonstrate striking responses to low gravity as effected by tumbling.

For a brief review of the early studies performed by means of a klinostat with plant geotropisms, the reader is referred to the 1943 edition of Heilbrunn's *Outline of General Physiology* (pp. 580-584). For some reason, Heilbrunn did not include as adequate a review in later editions of this book. At the present time, the problems of weightlessness are being investigated by two laboratories which are tumbling plants in a klinostat in order to eliminate gravitational effects, while simultaneously centrifuging the klinostats themselves in order to produce various intensities of low gravity. These two laboratories are the one at North American Aviation in Downey, California, and the one at the Argone National Laboratory in Argone, Illinois.

The work at North American Aviation has been pursued by Dr. J. C. Finn, Jr. (from report as abstracted in *Handbook*, 1963, pp. B-6-1-10). He reports that with the cocklebur, *Xanthium pennsylvanecium*, a slower growth occurs at subgravity conditions. Moreover, as tumbled plants are exposed to lower and lower centrifugal fields, there occurs an increasing angle separating the petioles (branches which bear leaves) from the central stem. (Thus the plants subjected to the lowest gravitational statesgive the appearance of greater drooping.) Similar results were indicated with less intensive studies employing potato, sweet pepper, and okra plants. Other studies with this drooping phenomena, but without the accessory centrifugation, have been pursued for several years at Dartmouth College (Lyon, 1962, 1963a,b).

The work at Argone is concerned primarily with the rate of growth for small plants subjected to different orientations in extremely low centrifugal fields by means of klinostats. This work is directed by Dr. Solon A. Gordon, in collaboration with Dr. J. S. Miller and Dr. R. Dedolph.

With three different species, alterations were noted in the rate of growth as influenced by the orientation of the plants with respect to fields as low as 5×10^{-6} G. Although the rate was influenced by orientation, the direction of growth apparently was independent of spatial coordinates. A herb of the genus *Arabidopis*, which was grown from seed, demonstrated slower growth, fewer and smaller leaves, and delayed flowering at this field. At this low field, duckweed, *Spirodela polyrhiza*, exhibited faster growth with respect to the replication of fronds. With germinating oats, *Avena satira*, the rate of growth varied with the direction of this very small field. Those orientated with their stems facing toward the center of the centrifuge grew more slowly than those orientated outward. One of the major considerations in employing klinostats and centrifuges for work at these extremely low fields has been the engineering details involved in the elimination of minute vibrations.

These results with plants in klinostats are highly significant for space biology from two practical points of view. Plants are under consideration in various recycling procedures for space travel. If the findings are applicable to animal material, moreover, there will be effects of weightlessness which are not detectable from simulations involving merely reduced activity and immobilization. The likelihood that such is possible would be suggested from the very early work with frog eggs in which the nature of embryonic development was influenced by orientation with respect to normal gravity. Preliminary observations by the Argone group indicate that weightlessness as effected by the klinostat procedure evokes abnormal development of frog embryos. However, Dr. Gordon does not feel that the investigation performed by his group with tadpoles is presently of a sufficiently rigorous nature to merit a definitive comment as to the significance of the observations. If various types of living material can respond to these very low gravitational fields, then even a satellite experiment in which complete elimination of gravitational fields is desired for weightlessness studies would be extremely difficult.

Dr. Solon thinks that the response of growing material to these very low centrifugal fields is not on the level of structures so small as molecules or so large as organs. He feels that it is probably at the level somewhere between that of a few cells and that of parts of a single cell. There is no existing adequate proven theory to explain the influence of gravity, particularly low gravity, upon the development of plants. It is generally assumed that gravity indirectly influences the distribution of plant growth hormones (auxins) in such a manner that certain parts of the growing cells do have threshold concentrations of the auxin. Dr. Solon suggests that a sedimentation of mitochondria could be brought about by gravitational fields. The chemical activity of the mitochondria would set up gradients of electrical potential. This electrical potential would cause an electrophoretic migration of the auxin, so that an unequal distribution of the auxin would be brought about not by direct gravitational sedimentation of this chemical but as the result of electrical phenomena which follow gravitationally-induced sedimentation of other structures.

The results of the tumbling experiments by the Argone group have not yet been published. Work with tumbling of plant material at Dartmouth College has recently been published by Lyon (1962, 1963a,b). In these publications, Lyon suggests that rather than causing an unequal distribution of auxin, gravity, at least in the case of leaf drooping, causes instead an even distribution of the auxin.

At the present time, the work at Argone is proceeding along three lines. First, they are attempting to develop devices with a series of gimbals, so that material can be tumbled in several different directions at the same time, thus eliminating orientation with respect not only to gravity but also with respect to other possible factors, such as the magnetic fields. Second, Dr. Miller is attempting to determine the precise threshold for the G-responses to these very low fields. Third, Dr. Dedolph is attempting to investigate the origin and the effect of any gravitationally-induced bioelectrical potentials.

Two tumbling devices have been designed for use with mature vertebrate material (humans and fish). One of these devices was built at the NASA-Langley Research Center at Hampton, Virginia. The other was constructed at Lockheed Aircraft at Marietta, Georgia. Both of these tumbling devices were intended for negation of the otolith response to gravity and involved immersion of the subject in water during tumbling.

The NASA device was originally designed in 1958. The proposed nature of this simulator was briefly described by Gerathewohl (1961, p. 111). The axis of rotation for the tumbler was at ear-level with human subjects being rotated in a "head-over-heels" manner. Its longest period of operation was one hour. The simulator is no longer being used for research purposes (Floyd L. Thompson, personal communication, 1964). However, some of the results obtained with this device are described in a paper which, at the time of this writing, is not available, although it is now in press (Stone and Letko, 1964). Continued use of the NASA simulator apparently has been abandoned as a result of certain second-order effects (primarily fluctuations in ambient hydrostatic pressure) attributable to the instrument's design (Levine, personal communication, 1964, and publication, 1963).

The tumbling studies at Lockheed have been pursued under the direction of Dr. Raphael Levine. Actually two simulators were built at Lockheed. One was a small device employed for experiments with fish and as a pilot model for the larger simulator. The larger model was for use with human subjects (Levine, 1961a,b, 1963). Levine has performed experiments with only one human subject (himself). In these experiments, he was exposed for as long as fifteen minutes to actual simulated weightlessness. In addition to the subject, the device requires a staff of four: the operator, an engineer, an attending physician, and a recorder. Its operation involves a number of carefully thought out and rehearsed safety precautions designed to avoid any possible danger to the subject during tumbling. The axis of rotation extends from the center of the head to the toes and coincides with the axis of symmetry of the cylindrical tank.

The Lockheed simulator is ready for further studies, but it presently is not in use. Further investigations with this device will require outside funding. The Lockheed Corporation already has invested approximately $100,000 in the apparatus and preliminary studies.

In an interview with Dr. Levine, he expressed an interest in continuing studies with this device in order to investigate the influence of weightlessness upon the factors arising from the otolith response in human subjects. At the same time, he was conservative with respect to suggesting the advantages of this apparatus in preference to fixed immersion tanks for use with other aspects of weightlessness (*e.g.*, muscular, skeletal, cardiovascular). It was designed primarily for otolith studies, combined effects of otolith and musculo-skeletal hypostimulation, and the effect of various low-G loads upon the otolith apparatus (as effected by slight deviations of the head from the center of rotation). One of the possible difficulties involves bubbles of air which might develop in the gastrointestinal tract. No difficulties of this nature have been encountered in studies to date. Another possible difficulty which was considered was that of the heart flopping about in the chest cavity during rotation. No sensation indicative of this difficulty was encountered.

It would seem that some studies with a device such as the Lockheed simulator would be an almost essential adjunct to ground-based hypoactivity experiments. No other devices are currently available, other than actual space flights, which would influence the possible effects of any reflexes arising from the otoliths.

D. Indirect Information Obtained from Experiments with Chronic Increase of the Gravitational Load

Frequently it is possible to predict the effect of decreasing some environmental agent in terms of the response of organisms to an increase in the agent. The exposure of plants and animals to high gravitational loads, either by means of chronic centrifugation or by means of requirements to support extra weight, might, in certain instances, indicate the opposite effect to be expected during exposure to a sub-gravity or weightless environment. However, as various biological responses do not necessarily vary in direct proportion to the ambient gravitational field, any prophecy of the effects of low gravity on the basis of observations of high gravity must be of an extremely cautious nature.

1. *Centrifuge Experiments for Extrapolation of Results of Exposure to High Gravity*

The influence of chronic exposure to high gravity upon animals has been recently reviewed by the present author (Wunder and Lutherer, 1964). This review is presently in press and should be available by the time this survey is completed. That review includes most of the findings which are pertinent to this portion of the survey. Therefore, the reader is referred to it for further details and for a discussion of the effects of chronic centrifugation. Accordingly these considerations will be described only briefly at this time.

Any extrapolation of the results from centrifuge experiments is complicated by the fact that certain responses are frequently enhanced by slight intensities of centrifugation but discouraged by more intense fields. Thus the direction of certain gravitationally-influenced effects is difficult to predict at one field intensity on the basis of results at another field intensity. A further difficulty in applying most of the findings with chronic centrifugation to the problem of weightlessness is that the studies have been performed with growing organisms, so that many of the results would reflect the influence of gravity upon development but would not necessarily indicate the influence of weightlessness upon adult men who are no longer undergoing development. In many instances, these investigations were concerned rather with problems of growth than with problems of weightlessness.

There are three laboratories in this country which for some time have been actively pursuing studies with chronic centrifugation. There is the group at Emory University, which initially was concerned with the influence of high gravity upon the development of wheat seedlings (Miller, 1950; Gray and Edwards, 1955; Edwards and Gray, 1956). More recently, they have been concerned with the effects of this agent upon the growth of animal cells in tissue culture (Edwards, 1963). The group at the State University of Iowa initially pursued investigations with fly larvae (Wunder, 1955) and since have pursued investigations with mice (Wunder *et al.*, 1960a; Wunder 1962; Bird *et al.*, 1963), with hamsters (Briney and Wunder, 1962), with turtles (Dodge and Wunder, 1963), and more recently with fish, grasshoppers, and chameleons (Wunder and Lutherer, 1964). The group at the University of California at Davis for several years have been studying the growth, development, and selection of chickens and other fowl during successive generations of chronic centrifugation (Smith *et al.*, 1959; Smith and Kelly, 1963). A brief study with centrifuged mice, which is as yet unpublished, was pursued by Captain Duane Graveline during the time when he was at Wright-Patterson Field.

Other groups are initiating studies with chronic centrifugation. A group at the NASA-Ames Research Center at Moffett Field, California, are initiating studies with mammals and expect within a year to have a centrifuge in operation which, unlike the previous ones in studies of this type, will be able to operate continuously during the servicing and care of exposed animals (Oyama and Platt, 1964; Oyama and Platt, 1963; Neville and Feller, 1964; Oyama, personal communication, 1964). At the University of Texas in Dallas (Montgomery *et al.*, 1963), studies are being pursued with the growth of bacteria during centrifugation. Although the Dallas group have reported the influence of very high intensity gravitational fields, upon bacterial growth, they have not yet resolved the question of whether the results of centrifugation were actually explainable in terms of inertial field acting upon the bacterial cells or in terms of very high ambient hydrostatic pressures which were generated by the high fields acting upon the fluid of the bacterial media. The results published by the Dallas group could be quite misleading.

In Europe, three groups are known to be concerned with the problems of chronic centrifugation, and all three are working with rats. At Cambridge University, extensive studies have been completed but have been published only in abstract form (Matthews, 1955). However, certain of Matthew's findings have been described in correspondence with the author, who has noted this correspondence in his recent review (Wunder and Lutherer, 1964). Studies have been discontinued at Cambridge, but similar investigations are being continued by Steel (1962), who is presently at Cardiff, Wales. Interesting results have also been reported from Bucharest (Vrabiesco and Domilesco, 1962; Vrabiesco *et al.*, 1964).

A number of the findings from centrifuge studies supplement those obtained during various types of weightlessness simulation. Although sufficiently intense gravities will cause a slower growth, moderate intensities of centrifugation do apparently stimulate or encourage growth. The specific nature of the responses to high fields, particularly with respect to differential effects on various systems or organs, is somewhat scattered. These responses depend, in addition to the intensity of the field, upon a number of factors, including age, diet, size, and physical condition of the organisms under observation. It is known that moderate centrifugation can enhance the growth of supporting structures, such as the femur bone and the gastrocnemius muscle. On the other hand, sufficiently intense fields apparently restrict the mobility of the animal, causing a slower relative growth of these structures. With respect to enhancing the development of the gastrocnemius muscle, the most striking effect of gravity upon mice appears to be relative not so much to wet or dry muscle mass as to the concentration of noncollagen nitrogen (which is believed to be indicative of the concentration of contractile protein) for experimental animals as contrasted to the concentration for control animals of comparable size (Bird and Wunder, unpublished results). The hematocrit of mice, hamsters, and rats decreases after a week or more of exposure. This decrease is consistent with the increase in hematocrit observed during immersion or bed rest as a simulation of the opposite gravitational field. On the other hand, exposure of chickens over a number of weeks apparently results in some adjustment such that experimental animals exhibit increased hematocrit. Although there have been no chronic studies of the influence upon catechol-amine level in lower animals, Goodall (1962) reports that for relatively short exposure of human subjects there is an increase in urinary norepinephrine. This finding complements the observation of a decreased level with immersed subjects. Goodall also reports an increase in adrenalin level, but he thinks that such increase might be more of a psychological response. It has been suggested by the group in Bucharest that although sufficiently high fields will discourage processes of physical growth, they will at the same time accelerate rates of development with respect to such factors as the onset of puberty and the onset of aging.

There is some indication with both chickens and fish that prolonged exposure to altered fields will cause an adjustment in the threshold level for detection of gravity by otoliths. In some instances, both of these animals show postural disorientation during removal from the centrifuge for servicing and/or observation. Upon return to the artificial, high gravity of the centrifuges, the organisms show a normal response to enhanced fields.

2. *The Transfer of Organisms to Normal Gravity after Development in High Centrifugal Fields*

This approach involves the maintenance of plants or animals throughout their development in exaggerated gravitational fields. Those adjustments which animals would be expected to make to an alteration in gravitational field should cause the organisms, upon return to the lower field of the Earth's gravity, to respond in the same manner that normal animals respond to subgravity. This approach should be considered only a qualitative indication of the effect of subgravity and would be applicable only with respect to considerations which involve adjustment to gravity. It would not indicate any effects which result directly from purely physical factors. It should indicate only responses dependent upon those of an organism's properties which are themselves influenced in one way or another by the gravitational environment.

There have been relatively few investigations of this type. In most cases, such studies have just been a sideline to studies of development at high gravity. Such an approach, however, might prove quite useful in evaluating a number of the responses to weightlessness. At the present time, there is a group at Holloman Air Force Base, New Mexico, that is initiating studies of this type in the hope of eliciting the effects of weightlessness upon blood volume (Dr. Harold von Beckh, personal communication, 1964). What few studies of this nature have been completed are reviewed elsewhere by Wunder and Lutherer (1964).

Upon transfer to normal gravity, the centrifuged animals, if they have not yet completed their physical development, often will demonstrate a period of faster than normal growth. There is, however, no indication that such animals will actually demonstrate an appreciable increase in the final or limiting size beyond that which would be occasioned for animals maintained throughout their development at normal gravity. This faster growth has been interpreted as indicative of some type of greater efficiency. Perhaps, in order to compensate for the extra work the animal has to perform to oppose gravity-like forces during centrifugation, various adjustments are made, so that the remaining food materials (*i.e.*, those which are not required for the greater tax of gravitational work) are more readily available for processes related to growth.

This argument can be substantiated by the finding that certain experimental animals (particularly fruit fly larvae, Wunder *et al.*, 1960b) consume less oxygen after removal from the centrifuge than do control animals even though the experimental animals might be growing at a faster rate. This observayion is compatible with the suggestion that weightlessness may cause a lower metabolic rate. At the present time, however, it warns of another possible danger. If high gravity cuases an increased metabolic efficiency, will prolonged exposure to weightlessness result in a decreased metabolic deficiency? Upon return to the Earth's gravity, after prolonged voyage in space, cardiovascular difficulties compounded by additional metabolic deconditioning could be insurmountable if not adequately anticipated.

Another aspect of the metabolic change is the possible effect on the respiratory diaphragm. The possible immobilization of the diaphragm by reduction of gravitational pull on the abdominal viscera has already been mentioned. With a lower metabolic requirement, it is likely that there would be lower stimulus for contraction of the diaphragm to counteract this immobilization. Preliminary studies of mice removed from the centrifuge after one or two weeks of prolonged centrifugation and then permitted to continue their development for from two to three weeks at normal gravity indicate some atrophy of the diaphragm. Although there is little or no observable change in the wet mass of the diaphragm, those diaphragms from the animals returned to normal gravit" showed a much higher percent of water content, and their dry weight relative to that of body mass was less than either that of the control animals or that of animals which remained under centrifugation (Wunder and Lutherer, 1964, and unpublished results).

3. *Evolution of a New Strain or Species in a Different Inertial Field*

As animals which presently exist on Earth have evolved in that planet's almost constant gravitational intensity, nature has undoubtedly selected organisms which are well adapted to this particular field intensity. A strain of animals which has been bred with a selection imposed by ability to breed in a centrifuge should result in organisms which will in many respects react to normal gravity in the same way as a native to this planet would be expected to react to a lower gravitational environment. Unlike certain other physical agents (*e.g.*, radiation), new strains of animals would arise only indirectly as a result of this new environment. Any gravitational field which known life would be able to survive would not contain sufficiently large concentrations of gravitational energy to bring about changes on the molecular level (such as are believed necessary to cause genetic changes). However, those animals best suited for the altered gravitational intensity within the centrifuge would be those most likely to naturally survive that environment.

The Davis group (Burton *et al.*, 1963) have reported such a strain of chickens. After six generations of centrifugation, these animals are much better able to tolerate prolonged high inertial fields than are ordinary chickens.

4. *Extrapolations with Animals Required to Perform Greater Than Normal Work in Opposition to the Earth's Gravity*

On the basis of arguments similar to those for extrapolating the results with animals grown in high centrifugal fields, one might anticipate that any other condition requiring animals to face greater gravitational adversity gives some indication of results which, upon extrapolation to the weightless state, would be of predictive value. Essentially such an approach would have all the disadvantages of chronic centrifugation, but, in addition, it would simulate an altered gravitational effect in a manner different from that expected either upon subjection to a lessened or an enhanced inertial field. A comparison of the results from organisms exposed to this type of a condition with results from chronic centrifugation has been discussed in considerable detail elsewhere (Wunder and Lutherer, 1964). Should such an approach be employed, the best predictions probably could be obtained by requiring animals to do work that is primarily of a static nature (*e.g.*, supporting weighted packs) rather than work of a highly dynamic nature (*e.g.*, swimming or running).

One interesting result in this connection was the finding of Graveline and McCally (1963) that immersed subjects required to support weighted packs did not show the same enhancement of high urine flow that was found under other conditions of submersion. The pattern of growth for mice required to wear packs equal to their own weight demonstrated growth patterns which were quite similar to those of mice centrifuged at 2 G. Tulloh and Romberg (1963) observed, moreover, that weighted packs will stimulate the growth of various bones in lambs in much the same way as would be expected in high gravitational fields or as would not be expected in low gravitational fields.

III. GENERAL SUGGESTIONS AND CONCLUSIONS

A. *Need for Better Communication between Investigators*

The most serious shortcoming in attempts to investigate the biological and medical conditions of weightlessness is not the inadequacy of any given approach to the problem but rather the inadequacy of communication between investigators in the area. This shortcoming is not surprising. It undoubtedly is typical of many areas of research, particularly those stimulated by the present emphasis on space exploration, which are forced to expand from almost nonexistent areas to ones involving hundreds or even thousands of scientists. Most scientific disciplines have been able to develop at an orderly pace, so that workers in the area can be duly trained in the basic principles relevant to the field. In these circumstances, pertinent publications are readily available in books and journals. Although there have been in this country two symposia devoted to the problems of weightlessness, investigators still await a symposium which meets and needs of biological and medical scientists. It is necessary, moreover, that measures be taken whereby it will be possible for investigators to present the results of their research in well-edited, reputable journals having a shorter time delay for processing and publishing manuscripts than is now considered adequate for other areas.

1. *Lack of Basic Background*

No basic background of information and principles is available for this field as it is for other fields having undergone a more orderly development. Moreover, phenomena must be observed from a different and unfamiliar point of view. Most of the leaders and directors of research possess only a few years of experience with weightlessness research. By the standards of more established fields, they would be considered "beginners" or "amateurs." Although a good understanding is required of both the biological and physical sciences, the average investigator is fortunate if he possesses a fair grounding in but one of these disciplines. For example, a biologist may not realize that the results which he obtains from studies with organisms exposed to an altered gravitational state might result from pressure-induced artifacts. At the same time, a physicist might not realize that even though inactivity or resting does not alter the gravitational field applied to the individual, these conditions frequently stimulate certain of the effects of weightlessness. We are even handicapped by a misleading terminology which is largely based upon the assumptions of constant gravitational influence. Communication is further complicated by the fact that people of diverse interests or approaches have been called upon to work in the same field. It is not unusual that two people at the same institution are both unaware that the other is exploring essentially the same problems, though, perhaps, from a different point of view.

2. *Previous Symposia on Weightlessness*

In an attempt to remedy the need for better communication, two symposia concerned with weightlessness have been held under the auspices of the American Astronautical Society and published in book form (Benedikt, 1961; Benedikt and Halliburton, 1962). Neither of these symposia helped to sufficiently correct the situation. An attempt was made to cover all approaches to the problem of weightlessness. Unfortunately most of the physical papers were too technical--and in some cases too premature--in nature to be of use to the biologist. Ideally the papers published from these symposia ought to represent comprehensive reviews. Yet all two frequently the papers represented little more than progress reports, which would have been rejected by any journal of scientific reviews that maintained reasonable standards. Apart from the quality of the papers, their arrangement in publication form was not of the kind which would permit a broad view of the problems of low gravity.

The shortcomings of these two symposia ought not to reflect upon the participants or the moderators; rather they should be considered an indication of the difficulties involved in any attempt to make order out of chaos. In all likelihood, these symposia were an unsurmountable undertaking, in terms of the number of people who were in a position to devote adequate time and planning to the program.

3. *The Need for New and Different Symposia*

What is needed most is a symposium which is primarily concerned with the needs of biological and medical scientists but one which at the same time does not ignore the physical areas basic to their problems. It is proposed that the symposium open with a series of lectures which, when published, will constitute a review of the basic scientific knowledge required by scientists concerned with the biomedical problems of reduced gravity. The second part of the symposium should include a number of short papers submitted by workers in the area. Every attempt should be made to encourage participation by representatives from all branches of scientific knowledge.

The orientation lectures should consist of invited papers by leading scientists in the biological and physical areas. So as to insure maximum understanding by investigators of differing backgrounds, it is not enough that the men presenting these invited papers be only scientists of stature; they must also be scientists who enjoy substantial reputations as lecturers and teachers, men experienced in the art of conveying information. Some of the lectures should be concerned with explanations of the physical implications of gravity, mass, weightlessness, and other relevant physical phenomena. Another group of lectures should be devoted to explaining the shortcomings and assumptions of each method for the simulation lated by the present emphasis on space exploration, which are forced to expand from almost nonexistent areas to ones involving hundreds or even thousands of scientists. Most scientific disciplines have been able to develop at an orderly pace, so that workers in the area can be duly trained in the basic principles relevant to the field. In these circumstances, pertinent publications are readily available in books and journals. Although there have been in this country two symposia devoted to the problems of weightlessness, investigators still await a symposium which meets and needs of biological and medical scientists. It is necessary, moreover, that measures be taken whereby it will be possible for investigators to present the results of their research in well-edited, reputable journals having a shorter time delay for processing and publishing manuscripts than is now considered adequate for other areas.

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In addition to the invited papers, a series of short papers should be submitted by various investigators. These contributions should be of sufficient scope to indicate in abstract form not only the problems which are being pursued but also the institutions or concerns and individuals pursuing the work. All of these papers ought then to be printed in abstract form. After careful editing by impartial, competent editors, the papers which best represent quality work in the field should be printed in their entirety.

Participation by leaders from diverse areas of science would assure adequate discussion and consideration of the various problems and approaches presented. To assure and encourage such participation, perhaps certain scientific scholars could be engaged as consultants. Their primary responsibility would be to discuss and criticize each paper as it is presented. Another step toward encouraging broad participation would be to hold the meeting in conjunction with a national or international scientific meeting of the type which normally attracts scientists from many different areas of study. Although not usually attracting many of the medical scientists, the meetings of the American Association for the Advancement of Science probably would most nearly satisfy the requirement for wide participation. Recent space biology symposia at AAAS meetings, however, have not been outstanding successes.

4. *Distribution of Information*

Due to the rapid rate of development required in studies of weightlessness, a more satisfactory mode of disseminating information is imperative. At the present time, the journals which serve the needs of sciences enjoying a more leisurely progress are frequently too slow to satisfy the demands of a burgeoning new discipline. These journals are unable to publish the manuscripts submitted to them at a faster rate without sacrificing something in quality. Forming a separate or new journal devoted primarily to the discussion of problems of weightlessness would be a mistake. It would remove pertinent articles and findings from the scrutiny and interest of other scientists, and it might also encourage "empire building." It is proposed rather that certain appropriate, existing journals be subsidized. In this way, established, reputable journals would be enabled to perform both faster and more qualified editing of the papers concerned with gravitational phenomena.

There also exists the problem that many of the results of investigations appear only in the form of government reports. Many of these reports are not available even at those libraries which possess appropriate journals. Furthermore, a reader is not assured that a government report has been subjected to the same editorial scrutiny that one can ordinarily expect of an article appearing in a journal of high prestige; he is thus forced to serve as his own editorial board in evaluating each report. It is therefore advised that submission of unpublished or unpublishable reports not be considered a major step in the completion of commitments by government scientists, grantees, or research contractors. When the work is unclassified and is of interest to a wide audience, the final report should be constituted of reprints of articles which appeared in reputable journals.

B. *Long-Range Planning*

Another factor which is perhaps a more important consideration than the actual procedure employed in simulating weightlessness is the necessity for an orderliness and permanence to the program. It would be misleading to suppose that the government can correct, overnight, the results of decades of neglect of space science by massive overspending before the basic fields in question are given adequate support and time for orderly development. Some of the chaos and confusion which characterizes work in any of the space-related problems is undoubtedly connected to the fact that our military agencies were forced to shift from a position in which mention of space science was all but forbidden prior to 1957 to a program in which an attempt is made to solve all problems overnight. A transformation of this magnitude is hardly conducive to organizing sophisticated, definitive, research programs. More than anything else, it encourages expensive but "quick and dirty" studies, which often do not proceed beyond the exploratory stage. In order to attract and train the best personnel for careful, well-established research programs, guaranteed support to contractors and grantees over long periods of time is more important than the transitory support of more expensive but less stable research. This type of support does not attract the dedicated, conscientious scientist who is dissatisfied with a poorly done or half-done job. Military personnel should not enter such programs if their tour of duty is too short or their background too inadequate to permit them to make a definitive contribution.

This rapid on-and-off approach to research compounds the problems of communication. It forces one to jump into a problem and attempt its solution before an appropriate evaluation of previous research has been accomplished. At the present time, to cite just one example, there are at least two places which wish to initiate or have already initiated studies concerning the influence of simulated weightlessness upon tolerance to a high gravity. Such a study is nearing completion at the School of Aerospace Medicine at Brooks Field, Texas. A more orderly approach would permit delaying the new projects until it is possible to take full advantage of the findings and advice available from the study at the School of Aerospace Medicine.

C. Justification for Extensive Ground-Based Studies

Carefully performed basic studies of results of simulated weightlessness in ground-based laboratories are essential if investigators are to take advantage of biological data collected from space flights. When judged by conventional research standards, such investigations, even though quite expensive, represent an almost insignificant cost in comparison to the expense of biological experiments in spacecraft. A recent report (Williams *et al.*, 1963) listed a figure of \$384,131,000† as describing the cost of the Mercury Project. In a breakdown of the cost, it was noted that approximately sixty percent was devoted to hardware and thirty-two percent to a radio network for communication with the capsule; but the basic biological research necessary to support this project was not even given a separate category. Presumably all basic studies were included in the two percent devoted to support and development. From this very expensive study, there was collected what from the biologist's point of view would be considered exploratory or pilot data. Results were collected for eight subjects in space (six men and two chimpanzees). What this means is that approximately fifty million dollars was spent for each subject. In spite of this very expensive data, scarcely any definite, conclusive findings of the biological effect of weightlessness were obtained. There was, in addition, very little or no adequate control data to permit evaluation of the likelihood that the results could be attributable to anything more than artifacts of the procedure (Catterson *et al.*, 1963). At the same time, the reliability of some of the data collected from these flights has been severely questioned (Neuman, 1963). An estimated twenty billion dollars will be spent toward placing a man on the moon (Dryden, 1964).

One readily admits, of course, that the value of the space effort cannot be judged solely in terms of its contribution to basic biological data. Its contribution to the other sciences must also be considered. Such outstanding astrophysicists as Dr. James Van Allen have pointed out that until it is possible to place a qualified scientist on the moon, most physical data can be collected in a more economical manner

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†More recently figures as high as \$600,000,000 have been listed for the final cost of the Mercury Project.

by use of instrumented rather than manned spacecraft (summarized by Kellogg, 1962, p. 11:17-19.

The advantages of placing a scientist on the moon by 1970 as a part of the Apollo Project were discussed at the recent AAAS meetings in Cleveland (reviewed by Kaufmann, 1964). Dr. Harold C. Urey (1964), Nobel Prize winner in chemistry and Professor at Large for Chemistry at the University of California, expressed the opinion that the cost of the Apollo Project would be justified from the point of view of its value to science if it were possible to place a qualified scientist on the moon. He indicated that such a scientist should be a descriptive geologist with several years of post-doctoral experience, and, in addition, should possess a fair grounding in astronomy and the theories pertaining to the origin of the moon. Urey indicated that he did not feel that top physical fitness or experience as an airplane pilot would be essential to this scientist's duty. He further pointed out that the average astronaut could not obtain the desired background in science by short courses in geology or astronomy.

General Don Fleckinger (1964), USAF MC (retired), doubted that it would be possible for such a passenger to travel during the early flights to the moon. Fleckinger noted that the reliability of present spacecraft as well as that intended for the Apollo mission is such that it could afford to carry only those occupants who could serve as reliable crewmen. Under these circumstances, such a crew would be composed of astronauts who were experienced test-pilots before pursuing astronaut training. The likelihood of finding a person of excellent physical condition and yet one who also possesses an adequate background in both astronaut training and in scientific disciplines seems remote. Russian spacecraft are apparently able to carry passengers who are not trained test pilots (Tereshkova, 1964). It seems likely, however, that the only individuals without astronaut training who will be passengers in American spacecraft in the near future will be chimpanzees or other lower forms of life.

It is not necessarily the recommendation of this reviewer that scheduled space flights be delayed until it is possible to obtain more satisfactory scientific information. It should be recognized that the acquisition of new scientific information is but one small aspect or goal of the entire space effort. At the same time, however, it is recommended that the people representing the various aims of the space program consider whether or not these aims might not be better met by a slower and more orderly program. If it is intended that the acquisition of new biological information be one of the major goals of the space program, then the statement made recently by Dr.

Loren Carlson (1964) seems appropriate.

> In conclusion I think that it is clear that a series of ground-based experiments which simulate the space effects are essential to characterize the time course of the effect and to establish the nature [of] significant tests to be performed in space. The necessity for biological experiments in space depends on the demonstration that simulation is inadequate. Following this the experiments in space can be planned to yield meaningful data.

Although a more orderly development of the space program might yield hardware which is more reliable and better able to carry scientists into space with perhaps a somewhat lower cash outlay, there are still other factors which argue for an accelerated program. These include the timing of the space program in a manner which is coincident with the willingness of the tax payers to provide financial support, matters of national prestige, and military necessity. (One hopes that matters of national politics are not a consideration.) It is not the place of this reviewer to pass judgment on these considerations. Nonetheless it goes almost without saying that biologists favor a program designed to yield as much new knowledge as possible concerning the biomedical aspects of weightlessness.

D. Evaluation of Existing Approaches to Weightlessness

Few existing studies of weightlessness yield well-controlled, definitive results in the biological and medical areas. They all are made up of essentially exploratory experiments.

1. *Requirements for Definitive Experiments*

The two primary requirements for any definitive investigation are (1) that only one variable at a time is changed in any experiment, and (2) that sufficient data is obtained to yield statistically valid results. The first of these requirements is the most difficult to meet. Any method of simulating weightlessness usually imposes a number of artifacts or second-order effects which frequently are difficult to reproduce in the control animals, particularly if the researcher desires findings that are applicable to normal organisms.

The second requirement, that of statistically valid results, is somewhat easier to meet. This condition can, as a rule, be met whenever resources are adequate to permit a sufficiently large sample of observations. Reliability of the statistics also depends upon two properties of the sample. The first is that the sample be of a homogeneous nature. The second is that the population studied be of essentially the same type as that for which information is desired. In order to assure a large homogeneous sample, it would seem that military installations (or other institutions where investigators can call from a large sample of men of essentially the same background and conditioning) would be best suited for extensive weightlessness studies with humans.

To enhance homogeneity of a sample, biologists frequently employ litter-mate controls. As human litter-mates (or twins) are somewhat hard to come by, the feasibility of their use in experimental investigation is generally prohibited by considerations of cost. Perhaps, with equipment as expensive as that used in the space effort, the cost of obtaining human litter-mates would not be so great. The feasibility of employing twins so as to enhance the validity of controlled experiments should be considered for exposures to weightlessness simulation which involves the use of space vehicles.

2. *Inadequacies of Satellite Experiments*

Even the satellite experiments which have been performed to date cannot be considered of a definitive nature. Although its cause has not been definitely established, the orthostatic hypotension exhibited by American astronauts, it seems reasonable to assume, can be attributed to exposure to weightlessness. On the other hand, the suggestion by American (Katzberg, 1963) and Russian scientists (Arsen'yeva *et al.*, 1962; Glembotskiy and Parfenov, 1962) that effects observed at the cellular level with satellite experiments are attributable to weightlessness seems remote. All of the experiments were based upon comparison with ground-based control material, but adequate compensation was not made for the pattern of acceleration, the thermal pattern of heating as the satellite passes through the atmosphere, various types of radiation (the action of which, particularly with some of the large bare, atomic nuclei, is not well understood), vibration, effects of change in the magnetic field, and possible unknown factors. The possibility that there are unknown factors in space which might be of biological consequence should not be overlooked; the existence of cosmic rays has been known only for sixty years and that of the radiation belts for less than ten years. In order to correct for these various factors, it is essential that the control material in weightlessness studies be placed in the satellite and centrifuged at one G.

There have even been statements in what one might assume to be a reliable journal (*Bulletin of the Institute of Biological Sciences*, 12:75, 1962) which suggest, on the basis of poorly controlled satellite experiments, the possibility that prolonged weightlessness will affect human cells. Extreme care must be taken to avoid suggesting that results of satellite experiments are necessarily attributable to weightlessness. These statements are highly publicized and are almost certain to be believed by the public. Should more careful studies show these premature reports to be invalid, both the scientific community and the space program are likely to suffer a regretable loss of prestige.

The reviewer has already indicated that centrifugation of control subjects within the satellite is the only satisfactory type of control condition for satellite experiments. One of the Russian groups which reported possible cellular effects suggested a number of different gound-based controls. However, they did not consider the possibility of actually centrifuging control material in the satellite (Glembotskiy and Parfenov, 1962). As the generation of one G of centrifugal field would require a relatively slow speed, this would pose little difficulty in working with cellular material and small plants.

With man and other animals, the use of a centrifuge, in addition to adding to the required size and weight for a satellite, would impose various second-order effects of rotation. Due to limitations of size, animals smaller than man would be more feasible as centrifuged control subjects. Hill and Schnitzer (1962) have discussed some of the limitations of a rotating space station. Their figures indicate that a rotating system which would be comfortable to man in creating a field of one G would have a rotational radius of almost two hundred feet, a rotational rate of four per minute, and a change in gravitational field from head to foot of approximately three and one-half percent. A preliminary report from Douglas Aircraft of Santa Monica, Californai (Collier, 1964) suggests that a rotating station with a radius of less than ten feet might prove adequate. The possible effects of rotation upon urinary changes in man is itself currently being investigated by General Dynamics at San Diego, California (Goble and Newsom, 1964).

E. Relationships between Intensity and Duration

There exists a need for better quantitative relationships between the response to weightlessness, the duration of exposure, and the extent to which these various factors simulate weightlessness. Some of the arguments justifying the need for these relationships have been discussed elsewhere (Carlson, 1964). Although satellite experiments do show that it is possible for man to survive in a weightless state for a period of four days, we are not in a position to place an upper limit upon this time, nor are we in a position to predict the magnitude of precautions necessary in order to avoid various deleterious effects of weightlessness. There is no reason for assuming that exposure to a situation which would reduce the gravitational load to one-half its normal value would necessarily yield the given deleterious effects of weightlessness in twice the time that would be required in a weightless state. Exercise studies during bed rest or immobilization indicate that something more complex than a linear relationship exists.

In connection with quantitative relationships between the magnitude and time of exposure and the degree of response, it is also necessary, for the sake of statistical evaluation of measured results, to obtain quantitative information with respect to the variability of these responses. In many laboratory investigations, it is assumed that the frequency distributions involved are closely approximated by a normal distribution. There is good reason for accepting such an incompletely explored assumption when determination of the exact nature of a frequency distribution for a given item might entail much more expense than the actual experiment itself. As was indicated previously, the cost of ground-based studies is relatively insignificant in comparison to costs for measurements which can be made in a satellite. For this reason, as much information as possible should be obtained concerning the variability of response to conditions related to weightlessness. A pattern of this variability would be indispensable in evaluating the differences between satellite and control data.

It would also be highly desirable to determine all the factors which cause a variation in response to a condition approximating weightlessness. Thus far, hypoactivity studies with men have not taken into consideration the various factors which could cause a variability in the response. The status of research in this area is such that an attempt to delve into the source of this variability would be premature. A homogeneous sample is necessary in order to establish just what trends do exist. Once these trends are well established, the next step should be to determine how such factors as diet, physical conditioning, size, age, racial background, and sex influence the symptoms of response to weightlessness.

F. *Placing Subjects within Carefully Programmed Robots*

There can be no denying that a completely adequate answer to the influence of weightlessness upon living material can be determined only in a large manned orbiting laboratory. The costs of such studies will be very great, and the date at which they may be properly pursued is remote. In the light of such difficulties and the anticipated expenses, it is reasonable to consider various methods of simulation which otherwise would seem too fantastic to justify the expenses involved.

As an example of such a device, it is proposed that we consider a carefully instrumented robot programmed by computing equipment. The subject would be placed inside of the robot and in all likelihood would be suspended by water contained within the robot. The robot would be shaped to enclose the entire body, with the robot's various parts attached by joints or couplings, so that these parts can experience essentially the same motion as that which is experineced by the member of the body enclosed within. The robot would be so instrumented and programmed that a slight movement by the subject housed within it would be detected and cause a motion of the external part of the robot by means of remote control. The programming of the robot would be such that the various movements experienced would be those expected from mechanical considerations for a body possessing specified inertial properties when placed within a gravitational field.. It is conceivable that such a program might be possible for various gravitational states, varying from that found on Earth to that of a completely weightless condition. Programs could be devised, moreover, which would include various frictional factors to test the differences expected from various types of clothing or pressure suits. The control subjects would be within identical robots programmed for the Earth's gravity. Although considerable development would be necessary before such a device could become a reality, certain inertial properties of the human body have been recently investigated (Whitsett, 1964).

A robot such as the one proposed would overcome the primary shortcoming* of all weightlessness simulation, which is that it depends upon inactivity, restriction, or immobilization. All of these procedures assume that lack of motion will have essentially the same effect as lack of gravitational force. This robot would permit the same amount of motion as would be possible in a low gravity state but would simulate a condition in which the moving parts would experience less gravitational force to oppose their motion than is conventionally experienced on this planet. Thermal controls could perhaps correct for the abnormal heat exchange occuring during immersion.

G. *Suggested Priority for Existing Ground-Based Approaches to Weightlessness*

As previously indicated, the primary factors in the approaches to the problem of weightlessness are the need for better communication, long-range planning, and training of investigators with respect to scientific background in the physical and biological areas. All of the approaches should possess, as a logical step in the development of their programs, quantitative relationships describing magnitudes, timing, degree of weightlessness, and reasons for differences in response to weightlessness.

1. *Basic Studies with Plants and Animals*

As an aid in evaluating and designing studies with man, there is a need for more basic studies with plants and animals. One largely overlooked method of investigating responses to reduced gravity is the study of material after removal from centrifugation. Such an approach should be used wherever feasible with all types of living material that will be subjected to the more expensive experiments requiring the use of a satellite.†

Another requirement is the necessity for resolving the unlikely possibility that weightlessness will affect animals at the cellular level. Should weightlessness have a significant effect upon cellular structure, then essentially all of the ground-based approaches to weightlessness, with the possible exception of tumbling, might prove woefully inadequate for human studies. It is suggested that every attempt be made to expand, accelerate, and thoroughly investigate the approaches to weightlessness which are presently being pursued by means of tumbling devices at the Argone National Laboratories. It is urged that such studies be expanded or implemented in such a way that animal cytologists and embryologists who are well grounded in physical theory avail themselves of the findings and techniques pursued in this project.

2. *Studies Involving Decreased Gravitational Load*

Of the studies presently being pursued with humans, it would seem that immersion comes the closest to actually simulating the weightless condition. Before full reliance

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†It should be recognized that this opinion could be biased by the reviewer's interest in and association with studies of chronic centrifugation.

can be placed upon this approach, however, two possible limitations must be removed. These involve (1) the second-order effects upon blood volume as a result of the type of respiration and (2) the unnatural type of heat exchange. Within limits, these limitations probably can be overcome by appropriate control conditions.

Some attempts should also be made to resolve the difficulty that with immersion studies, as with bed rest studies, appropriate basic investigations with animals are somewhat impractical. Although the Polish workers Walawski and Kaleta (1963) have described a study involving rabbits, this form as well as most other common laboratory mammals cannot be maintained with equal ease in either water or on land at the will of the investigator. Mammals which might prove adequate in such studies are the nutria, the muskrat, the beaver, and the seal. Suitable birds are the penguin, the loon, the comorant, and the water turkey or ahinga. Among potentially suitable reptiles are the alligator and the marine iguana. The tiger salamander and the toad might prove to be satisfactory amphibians. Even with fish, the gobi mudskipper (mudflat fish) and the walking perch might be satisfactory.†

A large-scale approach to the problems of weightlessness by means of immersion should probably entail some use of a tumbling device such as the Lockheed Simulator. This device could in all probability detect effects resulting from unsuspected reflexes arising in the otolith or even certain cellular effects. It should be recognized, however, that with the use of such an apparatus a restriction of permissible head movements might pose an insurmountable problem for studies involving prolonged exposure.

If the two primary limitations of water immersion studies cannot be overcome, then priority should be given to bed rest studies. This would not permit the degree of near-weightless movements possible during immersion; however, it would still permit certain of these movements which would not be possible during more rigid immobilization. Moreover, as bed rest is one of the most common forms of clinical treatment, such findings would be of obvious value to medicine.

Due to the fact that there are many dissimilarities between the influence of immobilization by means of plaster

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†The author is indebted to Dr. G. Edgar Folk, Jr. for suggesting most of these proposed animals.

casts or splints and the expected influence of weightlessness, immobilization approaches should receive a lower priority, except for certain studies with animals involving tenotomy. On the other hand, if the programs in immobilization research are intended to be of a wider application, then there is justification for their pursuit. Immobilization, when compared with other states of low gravity, could serve as an important source of new information for people concerned with therapy and rehabilitation. Plaster-casts-immobilization studies should occupy a relatively minor role in a program in which the primary goals are directed specifically toward the effects of weightlessness during space travel. They would, however, form an integral part of a broader program concerned with all aspects of hypoactivity and resulting debilitation.

IV. SUMMARY

The introduction briefly reviews the history, sources of available literature, possible effects, and confusing terminology associated with the biological consequences of a low gravity environment.

The central emphasis of the survey concerns the status of research involving various methods of effecting chronic weightlessness for organisms. Three general types of approach are considered: (1) accelerations that oppose the Earth's gravity, (2) indirect reduction of gravitational effects, and (3) indirect information from increases of gravitational load.

After initiation of this survey, the Air Force requested particular consideration of immobilization as one type of approach to the problems of weightlessness simulation. Immobilization (by means of casts, splints, tenotomy, and denervation) is considered as one aspect of the second category listed above. Other aspects of that category are bed rest, support by frictionless devices, buoyant support (during water immersion), and tumbling.

Specific suggestions are made with respect to the value of immobilization. Its value as a simulation of a low-gravity environment is questioned for several reasons. The primary objection is that immobilization tends to cause the type of low activity which is characterized by reduced external motion. In contrast to immobilization, a weightless environment, although requiring less work for a given quantity of motion, would not necessarily prevent external motion and might even permit greater amounts of such motion. The respiratory-diaphragm muscle is suggested as one of the few structures likely to be immobilized by weightlessness. At the same time, studies of immobilization should be encouraged for other reasons, some of which are related to restrictions that could be imposed by the small size of existing or proposed space capsules. The findings of such studies should not be confused with those necessarily predicting the effect of true weightlessness.

The following general suggestions are made concerning the nation's programs that are exploring the biological effects of weightlessness.

(1) Lack of adequate communication and lack of long-range planning are major deficiencies of the programs.

(2) Extreme caution must be exercise in interpreting the results of past and of presently planned satellite experiments with respect to the possible effects of weightlessness. Improved control conditions will be necessary.

(3) Acceleration of ground-based studies, even at the cost of delaying certain space flights, is a possible prerequisite of increasing the total value of biological information extracted from such flights.

(4) Buoyancy (water immersion) studies appear to be the best of the simple, ground-based simulations of low gravity for man. If corrections for certain artifacts of submersion are possible, then immersion is recommended as the approach to receive the highest priority with human subjects.

V. ACKNOWLEDGEMENTS

The author wishes to acknowledge a sincere debt of gratitude to the many investigators working in the area of weightlessness for their help and cooperation in the preparation of this manuscript. Due to the newness and diversity of these studies and the time limitations imposed, an adequate review of pertinent material would have been almost impossible if reliance were placed entirely upon published journals and conventional abstracting or indexing services. For this reason, a direct appeal was made to over one hundred investigators by means of correspondence, telephone conversations, and direct visits. Their response and cooperation was most helpful and heartwarming.

I am particularly indebted to the following individuals who not only shared their own knowledge with me but also reviewed for me certain portions of this manuscript: Capt. Jack Goldman, Capt. R. S. Kellogg, Dr. Raphael Levine, Col. Earl Brannon, Dr. Lawrence Lamb, Capt. Duane Graveline, Capt. Noel Hunt, III, Capt. Daniel Trophy, Dr. C. C. Cain, Dr. J. D. Thomson, Dr. Adrian Flatt, and Mr. Brian Duling. Acknowledgement should also be made to those individuals who assisted the author in library research and manuscript preparation: Mr. Lorenz Lutherer, Mrs. Erika Brown, and Mr. Dean Eberly. The author also wishes to thank Miss Catharine J. Reynolds (Head, Government Documents Library, State University of Iowa) and Miss Nina Frohwein (Medical Librarian, State University of Iowa), together with their staffs for their kindness in locating many relatively inaccessible government reports and articles.

The preparation of this survey was supported in part by U. S. Air Force contract No. AF 18(600)-2057 to the University of Virginia (administered by Dr. Frank Banghart) from Andrews Air Force Base (monitored by Dr. Albert W. Hetherington). Findings reported here from the author's laboratory have been sponsored in part by a series of grants to the State University of Iowa from the National Institutes of Health and the American Cancer Society. The author is presently a NIH Research Career Development Awardee and has pursued the present survey with the permission and approval of the National Institutes of Health.

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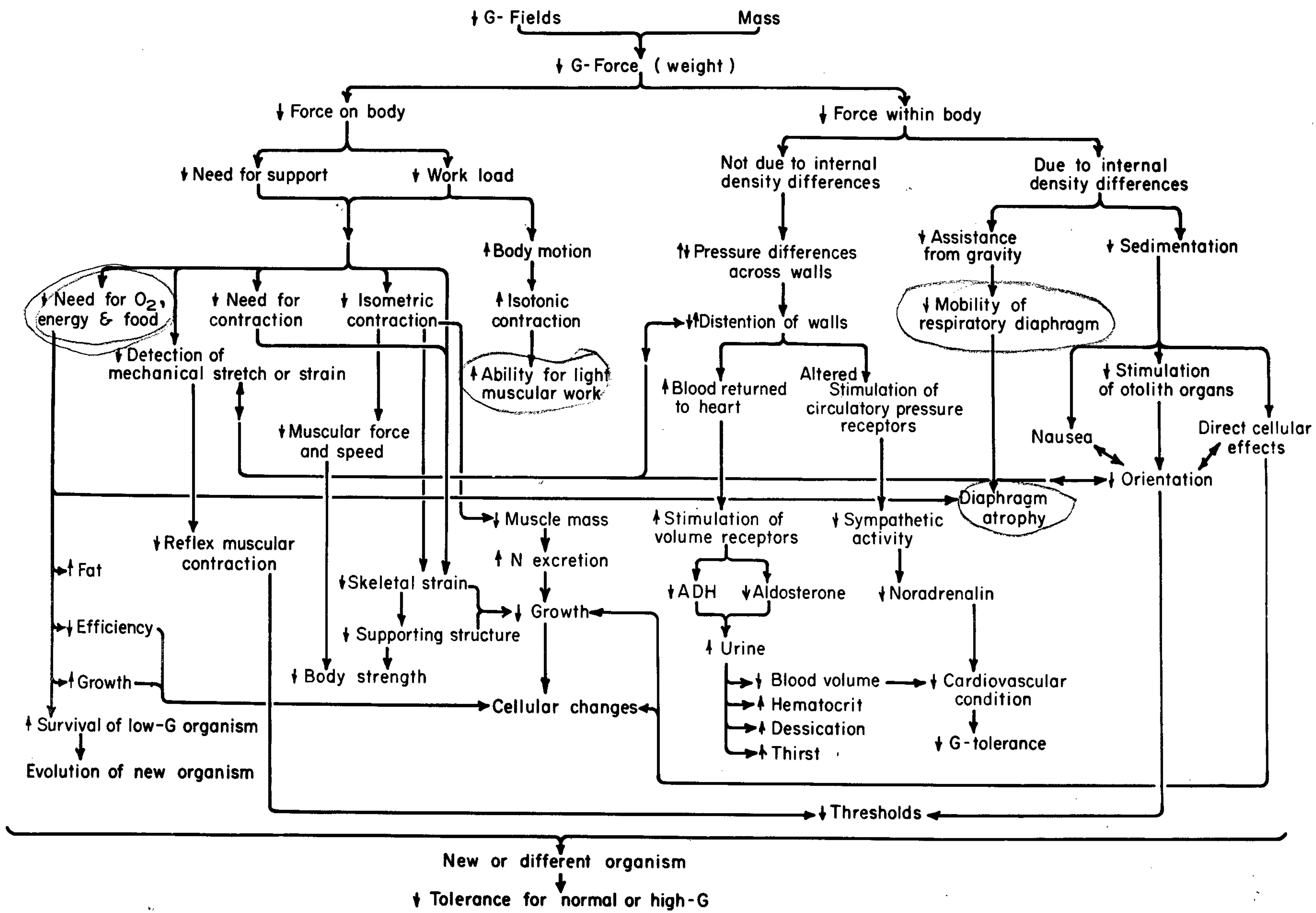

Fig. I. Some Possible Effects of Weightlessness

TABLE I

EFFECTS OF WEIGHTLESSNESS TO BE PREDICTED
FROM VARIOUS TYPES OF SIMULATION

Arrows indicate direction of changes; slanted arrows indicate only slight changes.

References are given to an article discussing or reviewing an experimental finding but not necessarily to the original publication which described the work. The references are as follows: 1) Allison and Brooks, 1921; 2) Birkhead *et al.*, 1963a; 3) Brannon *et al.*, 1963; 4) Catterson *et al.*, 1963; 5) Deitrick *et al.*, 1948; 6) Eccles, 1941; 7) Geiser and Trueta, 1958; 8) Dr. Jack Goldman, personal communication, 1964; 9) Goodall, 1962; 10) Graveline *et al.*, 1961; Graveline and McCally, 1963; 11) Graybiel and Clark, 1961; 12) *Handbook*, 1963 (in discussion of Finn's work); 13) Hawkins, 1963; 14) Heilbrunn, 1943; 15) Helander, 1960; 16) Henry *et al.*, 1952; Henry *et al.*, 1962; 17) Hines and Thomson, 1956; 18) Hislop, 1963; 19) Kas'yan, 1963; 20) Levine, 1963; 21) McCally, 1964; 22) McCally and Graveline, 1963a; 23) Parin, 1962; 24) Schottelius *et al.*, 1954; 25) Capt. J.C. Simons, personal communication, 1964; 26) Smith and Kelly, 1963; 27) Taylor *et al.*, 1945, 1949; 28) Thomson, 1955; 29) Volynkyn and Yajdovsky, 1962 (as cited by McCally, 1964); 30) von Beckh, 1954; 31) Vrabiesco *et al.*, 1964; 32) White and Berry, 1964; 33) Wunder and Lutherer, 1964; 34) Zelená, 1963; 35) Lilly and Shurley, 1961; 36) Margaria, 1958; 37) Capt. R.S. Kellogg, personal communication, 1964.

Table I. Effect of Weightlessness to be Predicted from Various Types of Simulation

Kim?

		Metabolic Rate	Obesity	Growth	Bone	Ca Excretion	Joint Stiffness or Pain	Muscle: Size	Muscle: Force	N Excretion	Urine Volume	Thirst	Hematocrit	Noradrenalin (urinary level)	Heart Rate	Heart Size	Orthostatic Hypotension	Diaphragm Edema & loss of dry mass	Disorientation	Tendency to Semi-Fetal Position	Stretch Reflex (knee jerk)
FLIGHT	Orbital			↓ mass dessication 4		± 4			± 4		dessication 4	↑ 4	↑ 4		± 4,33 unstable 24,20		↑ 4,30		only 1st 30sec. 33,24,17	↑ 4	
	Suborbital & Parbolic																↑ 31		↑ 31,16	↑ 26	↑ 13,38
BED REST		↓ 28		↓ body ↓ mass 3		± 3 ↑ 2	↑ 3	↙ 2	↓ 3	↗ 28 ↓ 2	↑ 2 ± 3		↑ 28 ↓ 2		↗ 28 ↓ stroke volume	↑ 28	↑ 3,2,28				
IMMOBILIZATION	Cast, Splint etc.	↓ 5		↓ rabbit bone 7		↑ 5	↑ 5	↙ 19 ↙ 5	↓ 5	↑ 5	↑ 5		± 5		↗ 5	± 5	↑ 5				
	Tenotomy (animals)		↑ 15	↓ bone 7 muscle 35				↙ 25	↓ 25												
	Denervation (animals)			↓ bone 1				↙ 6,18	↓ 6,18									↑ 29			↑ humans 13
IMMERSION						↑ 10			↙ 10,11	↑ 10	↑ 10	↑ 10	↑ 22	↑ 23	± 10		↑ 10,23		↗ 36,37	↑ 8	
TUMBLING				↓ plants 12															↑ 21,14		
CHRONIC CENTRIFUGATION (animals)	Moderate *	↓ 32		↓ 34				↙ 34					↑ 32 34 ↓ 27	↑ acute humans 9							
	High *	↓ 32	↑ 34	↑ 34				↗ 34													
	After removal	↓ 34		↑ 34														↑ 34			

TABLE II (a)

CONDITIONS WHICH ACHIEVE SOME OF THE EFFECTS OF WEIGHTLESSNESS

CONDITION	DEGREE OF WEIGHTLESSNESS
1. Remoteness from all heavenly bodies.	Complete, save for natural or artificial gravity generated by the space vehicle containing living material.
2. Opposing acceleration or changing a body's motion just sufficiently to counterbalance the gravitational acceleration.	Complete to the extent that the applied acceleration is uniform with respect to distance, time, and direction.
2a. Orbital flight in an artificial satellite for which the satellite's centrifugal field just counterbalances the Earth's gravitational field.	Almost completely, particularly at the center of the satellite. However, spinning could generate centrifugal fields, and the opposing centrifugal and gravitational fields could disagree at the rim of a space station by 1.5×10^{-4} G per mile of the station's radius.
2b. Suborbital trajectory flight in the nose-cone of ballistic rockets.	Duration of only a few minutes (poor uniformity of field).
2c. Parabolic or Keplerian flight in high-performance aircraft.	Duration of approximately one minute (poor uniformity of field).

TABLE II (a) cont'd

CONDITIONS WHICH ACHIEVE SOME OF THE EFFECTS OF WEIGHTLESSNESS

DISADVANTAGES	REMARKS
Theoretically, the time is still several years in the future when this will be possible with living material. Spinning or any change of a space ship's motion would still effect gravity-like forces.	
Difficult to place sizable quantities of living material in this situation while maintaining spatial and temporal purity of the apparent gravitational field.	
Same as above. High fields must accompany going into and leaving orbit. Extreme care is necessary to assure that control animals are exposed to all the non-weightless aspects of orbital space flight, such as radiation, vibration, short bouts of acceleration, and heating due to reentry.	A well-controlled experiment would in all likelihood require that control material be exposed to the same space voyage as the experimental organisms. A one-G environment would be maintained by centrifuging the control organisms within the space vehicle.
Same as 2 and 2a above. Furthermore, the period of post- and pre-weightless acceleration is sizable in comparison to the actual period of weightlessness.	
Same as 2, 2a, and 2b above, save for the fact that experimental material can be somewhat more easily placed in this condition and be more readily available to the observer.	

TABLE II (b)

CONDITIONS WHICH ACHIEVE SOME OF THE EFFECTS OF WEIGHTLESSNESS

CONDITION	DEGREE OF WEIGHTLESSNESS
2d. Falling in drop towers or slides.	Duration of seconds or less (poor uniformity of field).
3. Reducing the influence of gravity without actually decreasing its magnitude.	The extent to which gravitational effect is reduced can only be qualitatively estimated; it cannot be accurately quantified.
3a. Reduction of activity or work load.	Perhaps a fair qualitative comparison from the aspect of weight support and work. However, weightlessness would not restrict that aspect of activity which is primarily motion (mass x velocity) rather than work (force x distance).
3a(1). Bed rest.	
3a(2). Suspension or support by frictionless devices.	

TABLE II (b) cont'd

CONDITIONS WHICH ACHIEVE SOME OF THE EFFECTS OF WEIGHTLESSNESS

DISADVANTAGES	REMARKS
Too short a period to detect many biological responses to weightlessness.	
Various methods of reducing gravitational effect do not act equally on all parts or systems of an organism. Moreover, these methods frequently impose various types of restriction upon an organism which would cause experimental artifacts.	Many studies, particularly the earlier ones, employing this approach were designed primarily to investigate factors other than the absence of gravity. For this reason, the type of control is not of the optimum type with respect to weightlessness.
A certain amount of activity would be necessary even in the absence of gravity. Absence of gravity would reduce the amount of force required to support force or weight (isometric muscle work or static work). However, one would not expect such a drastic effect upon actual motion (isotonic, muscle contraction or kinetic activity).	
	Assumption of the horizontal position would not merely reduce the work to support gravitational force. It would also reduce the effective height of columns of fluid (such as blood), thus reducing the hydrostatic pressure which could be imposed by gravity.
Would primarily be useful only in considerations of performance in evaluating responses to the absence of external gravitationally-imposed frictional forces.	

TABLE II (c)

CONDITIONS WHICH ACHIEVE SOME OF THE EFFECTS OF WEIGHTLESSNESS

CONDITION	DEGREE OF WEIGHTLESSNESS
3a(3). Immobilization by means of casts, splints, and tenotomy.	Only for a portion of a body.
3a(4). Denervation.	Only for the denervated portion of a body.
3a(4.1). Complete denervation.	
3a(4.2). Sensory denervation.	
3a(4.3). Motor denervation.	
3b. Buoyant support by means of water immersion to oppose gravitational forces.	Fairly good simulation of reduced force requirements for slow body movements, body support, and opposition of gravitationally-induced pressures.

TABLE II (c) cont'd

CONDITIONS WHICH ACHIEVE SOME OF THE EFFECTS OF WEIGHTLESSNESS

DISADVANTAGES	REMARKS
This might impose a greater reduction in movement and in sensations of strength or tension from the muscles or tendons than would be the case for true weightlessness. Imposes unnatural environment for immobilized subjects. Also in certain respects weightlessness would afford a certain freedom of movement which would have the opposite effect of immobilization.	
As in 3a(2) above, this would exaggerate the absence of sensory information and absence of muscle stimulation and movement beyond that of the weightless conditions. Also it would have effect only with respect to the specific denervated areas rather than the entire system, as would be the case for denervated muscles.	
Would permit less nervous control than occurs in the weightless state.	Achieved in experimental animal by complete sectioning of a nerve.
	Achieved in experimental vertebrates by sectioning the dorsal route of spinal nerves as they enter the spinal cord.
	Achieved in experimental vertebrates by sectioning the ventral route of spinal nerves as they leave the spinal cord.
A greater force would be necessary for fast body movements due to the greater viscosity for water than for air. Would not negate the gravitational effect upon structures (such as the otolith bodies	

TABLE II (d)

CONDITIONS WHICH ACHIEVE SOME OF THE EFFECTS OF WEIGHTLESSNESS

CONDITION	DEGREE OF WEIGHTLESSNESS
3c. Tumbling of a subject about an axis which is at right angles to gravitational vector with a speed of rotation such that no net sedimentation or settling of structures or materials occurs.	Nearly complete at center of rotation.
4. Studies of chronic exposure to high gravitational loads.	

TABLE II (d) cont'd

CONDITIONS WHICH ACHIEVE SOME OF THE EFFECTS OF WEIGHTLESSNESS

DISADVANTAGES	REMARKS
of the gravity-detecting end-organs or of air-filled spaces, such as the lungs) the specific gravity of which is different from that of the surrounding medium or structure. Moreover, unless air is applied at a positive pressure, more work would be required for ventilation of the lungs, and experimental artifacts would arise as a result of negative-pressure breathing. There are also the difficulties associated with an unnatural heat exchange and unnatural ambient environment for the skin. Additional psychological difficulties associated with isolation, sensory deprivation, and boredom can result.	
Centrifugal fields would occur with increasing distances from the axis of rotation or with increasing rates of rotation. Moreover, high rates of rotation can cause a certain amount of disorientation due to a bizarre stimulation of such sensory organs as the semicircular canals of the middle ear.	This method has been employed with plant material for approximately 100 years (Sachs, 1872). When combined with water immersion, it has been proposed for use with animal material. Rotation with a seated subject tumbling from head to foot has been attempted and abandoned at the NASA-Langley Installation. Rotation of a prone subject in a sideways direction has met with greater success and is still under development at Lockheed in Marietta, Georgia (Levine, 1961a,b; 1963).
Imposes many potential effects of rotation, such as uneven G fields.	It is necessary in such studies that the arm length of the centrifuge be large in comparison to animal size, animal motion, and rate of rotation.

TABLE II (e)

CONDITIONS WHICH ACHIEVE SOME OF THE EFFECTS OF WEIGHTLESSNESS

CONDITION	DEGREE OF WEIGHTLESSNESS
4a. Chronic centrifugation and extrapolation of results with the assumption that subgravity would evoke the opposite response.	Depends upon the extent to which a response to gravity would increase in a linear manner with field intensity.
4b. Removal from chronic centrifugation to a less intense field (normal gravity or one G).	Qualitative indication of effect of subgravity upon factors resulting from adjustment to gravity.
4c. High-gravity strain of organisms evoked by maintenance of surviving animals over generations of centrifugation.	Qualitative indication of effect of subgravity upon factors displaying best survival during gravitational adversities.

TABLE II (e) cont'd

CONDITIONS WHICH ACHIEVE SOME OF THE EFFECTS OF WEIGHTLESSNESS

DISADVANTAGES	REMARKS
Not all of the responses observed in these studies are of the type which increase linearly with gravity. Biological growth is frequently enhanced by slight intensities of centrifugation but is discouraged by more intense fields (Wunder and Lutherer, 1964).	Most of these studies have been performed with growing animals, so that many of the results reflect the influence of gravity upon development but would not necessarily indicate the influence of weightlessness upon adult men. In many instances, these investigations were directed rather toward the problems of growth than those of weightlessness.
Would not indicate any effects which result directly from less gravitational force. It should indicate only the response due to properties which can be influenced in one way or another by the gravitational environment itself.	Involves developing or breeding organisms into a special organism possessing exaggerated characteristics. These organisms should respond to normal gravity in the same manner as normal animals should respond to subgravity.
Same as 4b above.	